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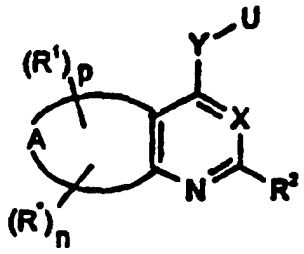
(54) Title: BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

(57) Abstract

Substituted heteroaromatic compounds, and in particular substituted bicyclic heteroaromatic compounds of formula (I), wherein X is N or CH; A represents a fused 5, 6 or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N, O or $S(O)_m$, wherein m is as defined above, the heterocyclic ring containing a total of 1, 2 or 3 double bonds inclusive of the bond in the pyridine or pyrimidine ring to which it is fused, with the provisos that the heterocyclic ring does not form part of a purine and that the fused heterocyclic ring does not contain two adjacent O or $S(O)_m$ atoms. U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and $S(O)_m$, wherein m is 0,1 or 2 and wherein the ring system is substituted by at least one independently selected R^6 group and is optionally substituted by at least one indepenently selected R^4 group, with the proviso that U does not represent phenyl; are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis.



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BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS

The present invention relates to a series of substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to bioisosteres of quinoline and quinazoline derivatives which exhibit protein tyrosine kinase inhibition.

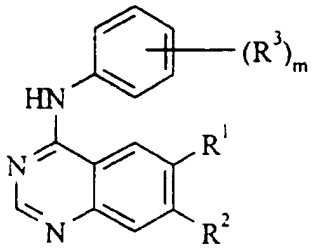
Protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A.F. Wilks, Progress in Growth Factor Research, 1990, 2, 97-111; S.A. Courtneidge, Dev. Supp.l, 1993, 57-64; J.A. Cooper, Semin. Cell Biol., 1994, 5(6), 377-387; R.F. Paulson, Semin. Immunol., 1995, 7(4), 267-277; A.C. Chan, Curr. Opin. Immunol., 1996, 8(3), 394-401). Protein tyrosine kinases can be broadly classified as receptor (e.g. EGFr, c-erbB-2, c-met, tie-2, PDGFr, FGFr) or non-receptor (e.g. c-src, lck, Zap70) kinases. Inappropriate or uncontrolled activation of many of these kinase, i.e. aberrant protein tyrosine kinase activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth.

Aberrant activity of protein tyrosine kinases, such as c-erbB-2, c-src, c-met, EGFr and PDGFr have been implicated in human malignancies. Elevated EGFr activity has, for example, been implicated in non-small cell lung, bladder and head and neck cancers, and increased c-erbB-2 activity in breast, ovarian, gastric and pancreatic cancers. Inhibition of protein tyrosine kinases should therefore provide a treatment for tumours such as those outlined above.

Aberrant protein tyrosine kinase activity has also been implicated in a variety of other disorders: psoriasis, (Dvir et al, J.Cell.Biol; 1991, 113, 857-865), fibrosis, atherosclerosis, restenosis, (Buchdunger et al, Proc.Natl.Acad.Sci. USA; 1991, 92, 2258-2262), auto-immune disease, allergy, asthma, transplantation rejection (Klausner and Samelson, Cell; 1991, 64, 875-878), inflammation (Berkois, Blood; 1992, 79(9), 2446-2454), thrombosis (Salari et al, FEBS; 1990, 263(1), 104-108) and nervous system diseases (Ohmichi et al, Biochemistry, 1992, 31, 4034-4039). Inhibitors of the specific protein tyrosine kinases involved in these diseases eg PDGF-R in restenosis and EGF-R in psoriasis, should lead to novel therapies for such disorders. P56lck and zap 70 are indicated in disease conditions in which T

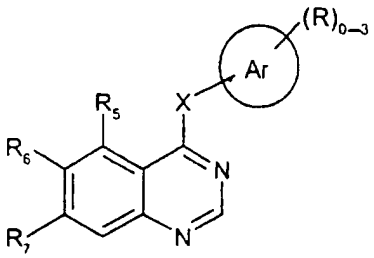
cells are hyperactive e.g. rheumatoid arthritis, autoimmune disease, allergy, asthma and graft rejection. The process of angiogenesis has been associated with a number of disease states (e.g. tumourogenesis, psoriasis, rheumatoid arthritis) and this has been shown to be controlled through the action of a number of receptor tyrosine kinases (L.K. Shawver, DDT, 1997, 2(2), 50-63).

EP0635507 discloses a class of tricyclic quinazoline derivatives of the formula:



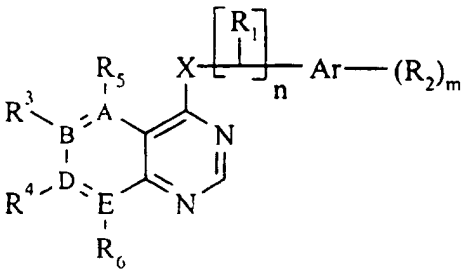
wherein R^1 and R^2 together form specified optionally substituted groups containing at least one heteroatom so as to form a 5 or 6-membered ring, in which there is a N atom at the 6 position of the quinazoline ring; R^3 includes independently hydrogen, hydroxy, halogeno, (1-4C)alkyl, (1-4C) alkoxy di-[(1-4C)alkyl]amino, or (2-4C)alkanoylamino. The above citation notes that receptor tyrosine kinases in general, which are important in the transmission of biochemical signals initiating cell replication, are frequently present at increased levels or with higher activities in common human cancers such as breast cancer (Sainsbury et al, Brit. J. Cancer, 1988, 58, 458). It is suggested that inhibitors of receptor tyrosine kinase should be of value as inhibitors of the growth of mammalian cancer cells (Yaish *et al.* Science, 1988, 242, 933). This citation therefore has the aim of providing quinazoline derivatives which inhibit receptor tyrosine kinases involved in controlling the tumourigenic phenotype.

WO 95/15758 discloses aryl and heteroaryl quinazoline derivatives of formula



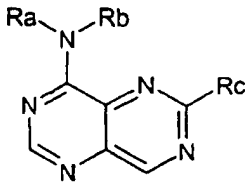
wherein X includes a bond, O, S, SO, SO_2, C≡C, C=C, CH_2 and NH; Ar includes phenyl, naphthyl, naphthalenyl, indolyl, pyridyl, piperidinyl, piperazinyl, dihydroquinolinyl, tetrahydroquinolinyl, thienyl, indanyl, pyrazolyl and 1,4-benzodioxanyl; and R_5, R_6 and R_7 independently include hydrogen, alkyl, alkylthio, cycloalkyl, hydroxy, alkoxy, aralkoxy, aryl, halo, haloalkyl, carboxy or carbalkoxy; as inhibitors of CSF-1R and/or p56lck receptor tyrosine kinase activity.

WO 95/19774 discloses bicyclic derivatives of formula:



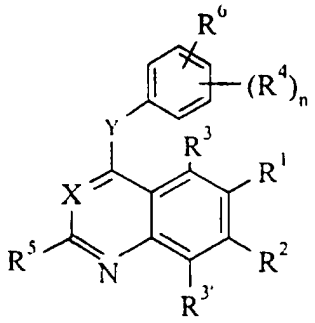
in which A to E are nitrogen or carbon and at least one of A to E is nitrogen; or two adjacent atoms together are N, O or S; R_1 is H or alkyl and n is 0, 1 or 2; m is 0 to 3 and R_2 includes optionally substituted alkyl, alkoxy, cycloalkoxy, cycloalkoxy, or two R_2 groups together form a carbocycle or heterocycle. The compounds are said to inhibit epidermal growth factor receptor tyrosine kinase and suggested uses include the treatment of cancer, psoriasis, kidney disease, pancreatitis and contraception.

WO 96/07657 discloses pyrimido[5,4-d]pyrimidine derivatives of formula



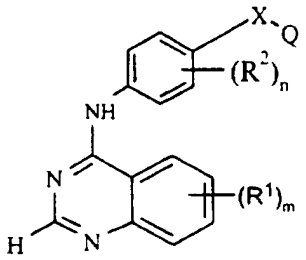
wherein Ra includes hydrogen or alkyl; Rb includes optionally substituted phenyl; and Rc includes hydrogen, halo, alkyl, cycloalkyl, cycloalkylalkylaryl, aralkyl, OH, optionally substituted alkoxy, cycloalkoxy, aryloxy, aralkoxy, mercapto, optionally substituted alkyl- or arylsulfenyl, -sulfinyl, or -sulfonyl and substituted alkyleneimino; as EGF-R inhibitors.

WO 96/09294 discloses quinoline and quinazoline derivatives of formula



wherein X is N or CH; Y includes O, S, CH_2O and NH; R^6 includes phenoxy, benzyloxy, benzylmercapto, benzylamino, benzyl, anilino, benzoyl, anilinocarbonyl, anilinomethyl, phenylethynyl, phenylethenyl, phenylethyl, phenylthio, phenylsulphonyl, benzylthio, benzylsulphonyl, phenylthiomethyl, phenylsulphonylmethyl, phenoxymethyl, thienylmethoxy, furanylmethoxy, cyclohexyl, and cyclohexylmethoxy; and R^1, R^2, R^3 and $R^{3'}$ include a range of possible substituents, predominantly not including heterocyclic ring systems; as protein receptor tyrosine kinase inhibitors, in particular as c-erbB-2 and/or p56lck inhibitors.

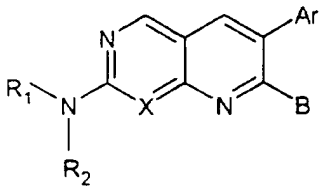
WO 96/15118 discloses quinazoline derivatives of formula



wherein X includes O, S, SO, SO_2, CH_2, OCH_2, CH_2O and CO; Q includes a phenyl or naphthyl group and various 5- or 6-membered heteroaryl moieties; n is 0, 1, 2 or 3

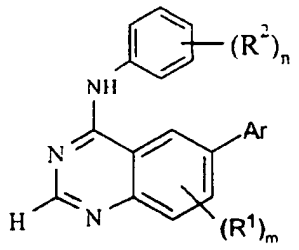
and each R^2 is independently halogeno, trifluoromethyl, hydroxy, amino, nitro, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, diC_{1-4} alkyl amino or C_{2-4} alkanoylamino; m is 1, 2 or 3 and R^1 includes a range of possible substituents, predominantly not including heterocyclic ring systems; as receptor tyrosine kinase inhibitors, in particular as EGF-R inhibitors.

WO 96/15128 discloses pyrido[2,3-d]pyrimidine and naphthyridine derivatives of formula



wherein X is CH or N; B is halo, hydroxy or NR_3R_4; Ar includes unsubstituted and substituted phenyl or pyridyl; and R_1, R_2, R_3 and R_4 independently include hydrogen, amino, C_{1-8}alkylamino, di-C_{1-8}alkylamino, unsubstituted and substituted aromatic or heteroaromatic groups, and unsubstituted and substituted C_{1-8}alkyl, C_{2-8}alkenyl or C_{2-8}alkynyl groups.

WO 96/16960 discloses quinazoline derivatives of formula



wherein m is 1 or 2; each R^1 independently includes hydrogen and C_{1-4}alkoxy; n is 1, 2 or 3; each R^2 independently includes hydrogen, halogeno and C_{1-4}alkyl, or R^2 is an aryl- or heteroaryl-containing group, including pyridylmethoxy and benzoyl; and Ar includes a substituted or unsubstituted 5- or 9-membered nitrogen-linked heteroaryl moiety containing up to four nitrogen atoms, in particular imidazol-1-yl, imidazolin-1-yl, benzimidazol-1-yl, pyrazol-1-yl and 1,2,4-triazol-1-yl; as receptor tyrosine kinase inhibitors, in particular as EGF-R inhibitors.

It is therefore a general object of the present invention to provide compounds suitable for the treatment of disorders mediated by protein tyrosine kinase activity, and in particular treatment of the above mentioned disorders.

In addition to the treatment of tumours, the present invention envisages that other disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition, including preferential inhibition, of the appropriate protein tyrosine kinase activity.

Broad spectrum inhibition of protein tyrosine kinase may not always provide optimal treatment of, for example tumours, and could in certain cases even be detrimental to subjects since protein tyrosine kinases provide an essential role in the normal regulation of cell growth.

It is another object of the present invention to provide compounds which preferentially inhibit protein tyrosine kinases, such as EGFr, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFr, c-src, Ick, Zap70, and fyn. There is also perceived to be a benefit in the preferential inhibition involving small groups of protein tyrosine kinases, for example c-erbB-2 and c-erbB-4 or c-erbB-2, c-erbB-4 and EGF-R.

A further object of the present invention is to provide compounds useful in the treatment of protein tyrosine kinase related diseases which minimise undesirable side-effects in the recipient.

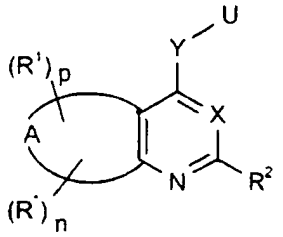
The present invention relates to heterocyclic compounds which may be used to treat disorders mediated by protein tyrosine kinases and in particular have anti-cancer properties. More particularly, the compounds of the present invention are potent inhibitors of protein tyrosine kinases such as such as EGFr, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFr, c-src, Ick, Zap70, and fyn, thereby allowing clinical management of particular diseased tissues.

The present invention envisages, in particular, the treatment of human malignancies, for example breast, non-small cell lung, ovary, stomach, and pancr atic tumours, especially those driven by EGFr or erbB-2, using the compounds of the present

invention. For example, the invention includes compounds which are highly active against the c-erbB-2 protein tyrosine kinase often in preference to the EGF receptor kinase hence allowing treatment of c-erbB-2 driven tumours. However, the invention also includes compounds which are highly active against both c-erbB-2 and EGF-R receptor kinases hence allowing treatment of a broader range of tumours.

More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a salt thereof;

wherein X is N or CH;

Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group;

R" represents a phenyl group or a 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms selected from N, O or $S(O)_m$, wherein m is as defined above, with the proviso that the ring does not contain two adjacent O or $S(O)_m$ atoms, the phenyl group or the heterocyclic ring being optionally substituted by one or more R^1 groups; and n = 0 or 1;

each R^1 is independently selected from the group comprising amino, hydrogen, halogen, hydroxy, nitro, carboxy, formyl, cyano, trifluoromethyl, trifluoromethoxy,

carbamoyl, ureido, guanidino, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkoxy, C_{4-8} alkylcycloalkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, N-C_{1-4} alkylcarbamoyl, N,N-di-[C_{1-4} alkyl]carbamoyl, hydroxyamino, C_{1-4} alkoxyamino, C_{2-4} alkanoyloxyamino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, di-[C_{1-4} alkyl]amino-C_{1-4} alkylene-(C_{1-4} alkyl)amino, C_{1-4} alkylamino- C_{1-4} alkylene-(C_{1-4} alkyl)amino, hydroxy-C_{1-4} alkylene-(C_{1-4} alkyl)amino, phenyl, phenoxy, 4-pyridon-1-yl, pyrrolidin-1-yl, imidazol-1-yl, piperidino, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, piperazin-1-yl, 4-C_{1-4} alkylpiperazin-1-yl, dioxolanyl, C_{1-8} alkylthio, arylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, arylsulphinyl, arylsulphonyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{2-4} alkanoyloxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, carboxy-C_{1-4} alkyl, formyl-C_{1-4} alkyl, C_{1-4} alkoxycarbonyl-C_{1-4}-alkyl, carbamoyl-C_{1-4} alkyl, N-C_{1-4} alkylcarbamoyl-C_{1-4}alkyl, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4}alkyl, amino-C_{1-4} alkyl, C_{1-4} alkylamino-C_{1-4} alkyl, di-[C_{1-4} alkyl]amino-C_{1-4} alkyl, phenyl-C_{1-4} alkyl, 4-pyridon-1-yl-C_{1-4} alkyl, pyrrolidin-1-yl-C_{1-4} alkyl, imidazol-1-yl-C_{1-4} alkyl, piperidino-C_{1-4} alkyl, morpholino-C_{1-4} alkyl, thiomorpholino-C_{1-4}alkyl, thiomorpholino-1-oxide-C_{1-4}alkyl, thiomorpholino-1,1-dioxide-C_{1-4}alkyl, piperazin-1-yl-C_{1-4}alkyl, 4-C_{1-4} alkylpiperazin-1-yl-C_{1-4} alkyl, hydroxy-C_{2-4} alkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkoxy-C_{1-4} alkyl, hydroxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, hydroxy-C_{2-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylthio-C_{1-4} alkyl, phenoxy-C_{1-4} alkyl, anilino-C_{1-4} alkyl, phenylthio-C_{1-4} alkyl, cyano-C_{1-4} alkyl, halogeno-C_{2-4} alkoxy, hydroxy-C_{2-4} alkoxy, C_{2-4} alkanoyloxy-C_{2-4} alkoxy, C_{1-4} alkoxy-C_{2-4} alkoxy, carboxy-C_{1-4} alkoxy, formyl-C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl-C_{1-4} alkoxy, carbamoyl-C_{1-4} alkoxy, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkoxy, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkoxy, amino-C_{2-4} alkoxy, C_{1-4} alkylamino-C_{2-4} alkoxy, di-[C_{1-4} alkyl]amino-C_{2-4} alkoxy, di-[C_{1-4} alkyl-C_{2-4} alkoxy]amino-C_{2-4} alkoxy, C_{2-4} alkanoyloxy, hydroxy-C_{2-4} alkanoyloxy, C_{1-4}alkoxy-C_{2-4} alkanoyloxy, phenyl-C_{1-4} alkoxy, phenoxy-C_{2-4} alkoxy, anilino-C_{2-4} alkoxy, phenylthio-C_{2-4} alkoxy, 4-pyridon-1-yl-C_{2-4} alkoxy, piperidino-C_{2-4} alkoxy, pyrrolidin-1-yl-C_{2-4} alkoxy, imidazol-1-yl-C_{2-4} alkoxy, morpholino-C_{2-4} alkoxy, thiomorpholino-C_{2-4} alkoxy, thiomorpholino-1-oxide-C_{2-4} alkoxy, thiomorpholino-1,1-dioxide-C_{2-4} alkoxy, piperazin-1-yl-C_{2-4} alkoxy, 4-C_{1-4} alkylpiperazin-1-yl-C_{2-4} alkoxy, halogeno-C_{2-4} alkylamino, hydroxy-C_{2-4} alkylamino, C_{2-4} alkanoyloxy-C_{2-4} alkylamino, C_{1-4} alkoxy-C_{2-4} alkylamino, carboxy-C_{1-4} alkylamino, C_{1-4} alkoxycarbonyl-C_{1-4} alkylamino, carbamoyl-C_{1-4}

alkylamino, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkylamino, amino-C_{2-4} alkylamino, C_{1-4} alkylamino-C_{2-4} alkylamino, di-[C_{1-4}alkyl]amino-C_{2-4} alkylamino, phenyl-C_{1-4} alkylamino, phenoxy-C_{2-4} alkylamino, anilino-C_{2-4} alkylamino, 4-pyridon-1-yl-C_{2-4} alkylamino, pyrrolidin-1-yl-C_{2-4} alkylamino, imidazol-1-yl-C_{2-4} alkylamino, piperidino-C_{2-4} alkylamino, morpholino-C_{2-4} alkylamino, thiomorpholino-C_{2-4} alkylamino, thiomorpholino-1-oxide-C_{2-4} alkylamino, thiomorpholino-1,1-dioxide-C_{2-4} alkylamino, piperazin-1-yl-C_{2-4} alkylamino, 4-(C_{1-4} alkyl)piperazin-1-yl-C_{2-4} alkylamino , phenylthio-C_{2-4} alkylamino, C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkylsulphonylamino, C_{1-4} alkylsulphinylamino, benzamido, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halogeno-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoyl-(C_{1-4} alkyl)-amino, C_{1-4} alkoxy-C_{2-4} alkanoylamino, carboxy-C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonyl-C_{2-4} alkanoylamino, carbamoyl-C_{2-4} alkanoylamino, N-C_{1-4} alkylcarbamoyl-C_{2-4} alkanoylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{2-4} alkanoylamino, amino-C_{2-4} alkanoylamino, C_{1-4} alkylamino-C_{2-4} alkanoylamino or di-[C_{1-4} alkyl]amino-C_{2-4} alkanoylamino, and wherein said benzamido or benzenesulphonamido substituent or any anilino, phenoxy or phenyl group on a R^1 substituent may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents; and wherein any substituent containing a heterocyclic ring may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents on said ring; and wherein any substituent containing a heterocyclic ring may optionally bear one or two oxo or thioxo substituents on said ring;

or R^1 represents a group selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 wherein

M^1 represents a C_{1-4} alkyl group, wherein optionally a CH_2 group is replaced by a CO group;

M^2 represents NR^{12} or $CR^{12}R^{13}$, in which R^{12} and R^{13} each independently represent H or C_{1-4} alkyl;

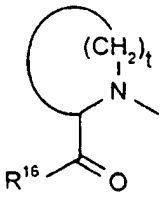
M^3 represents a C_{1-4} alkyl group;

$M^{3'}$ represents a C_{1-4} alkyl group or is absent;

M^4 represents CN, $NR^{12}S(O)_mR^{13}$, $S(O)_mNR^{14}R^{15}$, $CONR^{14}R^{15}$, $S(O)_mR^{13}$ or CO_2R^{13}, in which R^{12}, R^{13} and m are as hereinbefore defined and R^{14} and R^{15} each independently represent H or C_{1-4} alkyl, or R^{14} and R^{15} together with the nitrogen

atom to which they are attached represent a 5- or 6-membered ring optionally containing 1 or 2 additional heteroatoms selected from N, O or $S(O)_m$ in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, and which ring may optionally bear one or two oxo or thioxo substituents;

M^5 represents the group $NR^{14}R^{15}$, wherein R^{14} and R^{15} are as defined above, or M^5 represents the group



in which t represents 2 to 4 and R^{16} represents OH, OC_{1-4} alkyl or $NR^{14}R^{15}$; and

M^6 represents a C_{3-6} cycloalkyl group, the group $NR^{14}R^{15}$, wherein R^{14} and R^{15} are as defined above, or a 5- or 6-membered heterocyclic ring system containing 1 to 4 heteroatoms selected from N, O or S;

and p is 0 to 3; or when p is 2 or 3, two adjacent R^1 groups together form an optionally substituted methylenedioxy or ethylenedioxy group;

R^2 is selected from the group comprising hydrogen, halogen, trifluoromethyl, C_{1-4} alkyl and C_{1-4} alkoxy;

U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and $S(O)_m$, wherein m is 0,1 or 2 and wherein the ring system is substituted by at least one independently selected R^6 group and is optionally substituted by at least one independently selected R^4 group, with the proviso that U does not represent phenyl;

each R^4 is independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, di-[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, di-[C_{1-4} alkyl] carbamoyl, carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro or trifluoromethyl;

each R^6 is independently a group ZR^7 wherein Z is joined to R^7 through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, V(CRR'), V(CHR) or V where R and R' are each C_{1-4} alkyl and in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, dicarbonyl, CH(OH), CH(CN), sulphonamide, amide, O, $S(O)_m$ or NR^b where R^b is hydrogen or R^b is C_{1-4} alkyl; and R^7 is an optionally substituted C_{3-6} cycloalkyl; or an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety;
or R^6 is a group ZR^7 in which Z is NR^b, and NR^b and R^7 together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety;

A represents a fused 5, 6 or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N, O or $S(O)_m$, wherein m is as defined above, the heterocyclic ring containing a total of 1, 2 or 3 double bonds inclusive of the bond in the pyridine or pyrimidine ring to which it is fused, with the provisos that the heterocyclic ring does not form part of a purine and that the fused heterocyclic ring does not contain two adjacent O or $S(O)_m$ atoms.

Solvates of the compounds of formula (I) are also included within the scope of the present invention.

Heterocyclic groups comprise one or more rings which may be saturated, unsaturated, or aromatic and which may independently contain one or more heteroatoms in each ring.

Carbocyclic groups comprise one or more rings which may be independently saturated, unsaturated, or aromatic and which contain only carbon and hydrogen.

Suitably the 5, 6, 7, 8, 9 or 10-membered heterocyclic moiety is selected from the group comprising: furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, quinazoline, quinoline, isoquinoline and ketal.

Suitably the 5, 6, 7, 8, 9 or 10-membered carbocyclic moiety is selected from the group comprising: phenyl, benzyl, indene, naphthalene, tetralin, decalin, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl.

By halo is meant fluoro, chloro, bromo or iodo.

Alkyl groups containing three or more carbon atoms may be straight, branched or cyclised.

In an embodiment R^1 is as defined above with the exception of wherein any substituent containing a heterocyclic ring bears one or two oxo or thioxo substituents on said ring; and R^{14} and R^{15} are as defined above with the exception of wherein they together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring and said ring bears one or two oxo or thioxo substituents; save that R^1 may represent 4-pyridon-1-yl, 4-pyridon-1-yl-C_{1-4} alkyl, 4-pyridon-1-yl-C_{2-4} alkoxy, 4-pyridon-1-yl-C_{2-4} alkylamino, 2-oxopyrrolidin-1-yl or 2,5-dioxopyrrolidin-1-yl.

In an embodiment, X is N.

In a further embodiment, Y is NR^b, $NR^b(CH_2)$, or $(CH_2)NR^b$, preferably Y is NR^b and R^b is preferably hydrogen or methyl.

In a further embodiment R'' is a 5- or 6-membered heterocyclic ring as defined above, optionally substituted by one or more R^1 groups selected from the group comprising amino, hydrogen, halogen, hydroxy, formyl, carboxy, cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylsulphinyl, C_{1-8} alkylsulphonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, dioxolanyl, hydroxy-C_{1-4} alkyl or hydroxy-C_{1-4} alkanoyl-(C_{1-4} alkyl)-amino.

In a further embodiment, n is 0 and each R^1 is selected from the group comprising amino, hydrogen, halogen, hydroxy, formyl, carboxy, cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylsulphinyl, C_{1-8} alkylsulphonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, dioxolanyl, benzyloxy or hydroxy-C_{1-4} alkanoyl-(C_{1-4} alkyl)-amino.

In a preferred embodiment, n is 0, p is 1 and R^1 is selected from the group comprising amino, C_{1-4} alkylamino, diC_{1-4} alkylamino, especially diC_{1-4} alkylamino, most especially dimethylamino or methylethylamino.

In a further embodiment, n is 0 and R^1 is selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above; and p = 1.

In a further embodiment R'' is a 5- or 6-membered heterocyclic ring as defined above substituted with an R^1 group selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above; and p = 0.

In a further embodiment the group M^2-M^3-M^4 represents an α-, β- or γ-amino carboxylic, sulphinic or sulphonic acid or a C_{1-4} alkyl ester, an amide or a C_{1-4} alkyl- or di-(C_{1-4} alkyl)-amide thereof.

Preferably M^1 represents CH_2, CO, CH_2CH_2 or CH_2CO, more preferably CH_2.

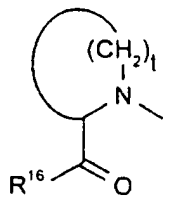
Preferably M^2 represents NR^{12} in which R^{12} is as defined above; more preferably R^{12} represents H or methyl.

Preferably M^3 represents CH_2, CH_2CH_2 or propyl.

Preferably $M^{3'}$ represents CH_2, ethyl, propyl, isopropyl or is absent.

Preferably M^4 represents SOR^{13}, SO_2R^{13}, $NR^{12}SO_2R^{13}$, CO_2R^{13} or $CONR^{14}R^{15}$ in which R^{12} and R^{13} are defined above and R^{14} and R^{15} each independently represent H or C_{1-4} alkyl; more preferably R^{12}, R^{13}, R^{14} and R^{15} each independently represent H or methyl.

Preferably M^5 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, preferably a methyl group; or M^5 represents a group



in which t represents 2 or 3 and R^{16} represents OH, NH_2, $N(C_{1-4}$ alkyl$)_2$ or OC_{1-4} alkyl; more preferably R^{16} represents NH_2 or $N(CH_3)_2$.

M^5 also preferably represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} each independently represent hydrogen or C_{1-4} alkyl, more preferably hydrogen, methyl, ethyl or isopropyl.

Preferably M^6 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} each independently represent C_{1-4} alkyl, more preferably methyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, preferably a methyl group; or M^6 represents a 5- or 6-membered heterocyclic ring system containing 1 or 2 heteroatoms selected from N or O.

In a further preferred embodiment M^2-M^3-M^4 represents an α-amino carboxylic acid or a methyl ester or amide thereof.

In a further preferred embodiment M^2-M^3-M^4 represents an α-, β- or γ-amino sulphinic or sulphonic acid, more preferably a β- or γ-amino sulphinic or sulphonic acid, most preferably a β-aminosulphonic acid, or a methyl ester thereof.

In an especially preferred embodiment M^2-M^3-M^4 represents a methylsulphonylethylamino, methylsulphinylethylamino, methylsulphonylpropylamino, methylsulphinylpropylamino, methylsulphonamidoethylamino, sarcosinamide, glycine, glycinamide, glycine methyl ester or acetylaminoethylamino group.

In a further especially preferred embodiment M^5 represents a piperazinyl, methylpiperazinyl, piperidinyl, prolinamido or *N,N*-dimethylprolinamido group.

In a further especially preferred embodiment M^5 represents an isopropylamino or N-morpholinyl group.

In a further especially preferred embodiment M^1-M^5 represents an isopropylacetamido or N-morpholinoacetamido group.

In a further especially preferred embodiment M^2-$M^{3'}$-M^6 represents a pyridylamino, cyclopropylamino, N-(piperidin-4-yl)-N-methylamino, N,N-dimethylaminoprop-2-ylamino, N-(2-dimethylaminoethyl)-N-ethylamino or tetrahydrofuranomethylamino group, preferably a pyridylamino group.

In an embodiment R" may be selected from the group comprising phenyl, furan, thiophene, pyridine, pyrimidine, pyrazine, pyrrole, oxazole, isoxazole, oxadiazole, thiazole, isothiazole, triazole, tetrazole and imidazole or a hydrogenated derivative of any of the aforementioned.

In a further preferred embodiment R" may be selected from the group comprising phenyl, furan, imidazole, tetrazole, triazole, pyrrolidine, piperazine, piperidine and oxadiazole.

In a further embodiment each R^1 is independently selected from the group comprising amino, hydrogen, halogen, hydroxy, formyl, carboxy, cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylsulphinyl, C_{1-8} alkylsulphonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, benzyloxy, hydroxy-C_{1-4} alkyl, hydroxy-C_{1-4} alkanoyl-(C_{1-4} alkyl)-amino.

In an embodiment R^2 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy or halogen, preferably methyl or hydrogen, more preferably hydrogen.

In a further embodiment R^4 is hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, di-[C_{1-4} alkyl]amino, nitro or trifluoromethyl, preferably hydrogen, halogen or methyl, more preferably hydrogen.

In a preferred embodiment R^7 is an optionally substituted phenyl, dioxolanyl, thienyl, cyclohexyl or pyridyl group.

In a further embodiment, Z is absent or represents oxygen, CH_2, NR^b, $NR^b(CH_2)$, $(CH_2)NR^b$, $CH(CH_3)$, $O(CH_2)$, (CH)CN, $O(CF_2)$, $(CH_2)O$, $(CF_2)O$, $S(CH_2)$, $S(O)_m$, carbonyl or dicarbonyl, wherein R^b is hydrogen or C_{1-4} alkyl.

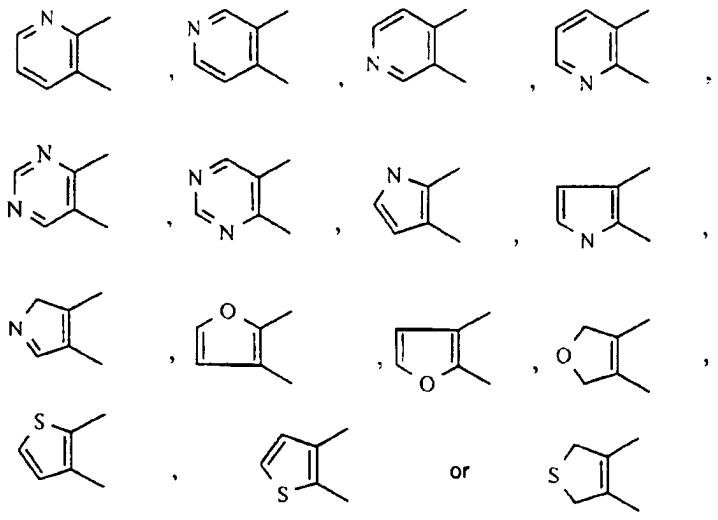
In a preferred embodiment Z is oxygen, dicarbonyl, OCH_2, $CH_2(CN)$, S(O)m or NR^b, wherein R^b is hydrogen or C_{1-4} alkyl.

In a further preferred embodiment R^6 is benzyl, , halo-, dihalo- and trihalobenzyl, α-methylbenzyl, phenyl, halo-, dihalo- and trihalophenyl, pyridyl, pyridylmethyl, pyridyloxy, pyridylmethoxy, thienylmethoxy, dioxolanylmethoxy, cyclohexylmethoxy, phenoxy, halo-, dihalo- and trihalophenoxy, phenylthio, benzyloxy, halo-, dihalo- and trihalobenzyloxy, C_{1-4} alkoxybenzyloxy, phenyloxalyl or benzenesulphonyl, more preferably benzyl, fluorobenzyl, benzyloxy, fluorobenzyloxy, pyridylmethyl, phenyl, benzenesulphonyl, phenoxy or fluorophenoxy.

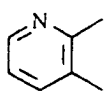
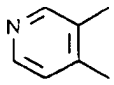
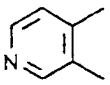
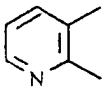
In a further embodiment R^6 is in the para position with respect to Y.

When the group Z is absent, $R^6 = R^7$.

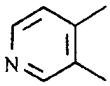
In a further embodiment A represents



; preferably

more preferably



One or both of the rings comprising the mono or bicyclic ring system U may be aromatic or non-aromatic. The R^4 and R^6 groups may be bound to the ring system by either a carbon atom or a heteroatom of the ring system. The ring system itself may be bound to the bridging group by a carbon atom or a heteroatom. The R^4 and R^6 groups may be bound to either ring when U represents a bicyclic ring system, but these groups are preferably bound to the ring which is not bound to the bridging group Y in such a case.

Examples of suitable mono or bicyclic groups U include: isoindenyl, indenyl, indanyl, naphthyl, 1,2-dihydronaphthyl or 1,2,3,4-tetrahydronaphthyl, pyrrolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furanyl, 2H-pyranyl, thiophenyl, 1H-azepinyl, oxepinyl, thiepinyl, azocinyl, 2H-oxocinyl, thieno[2,3-b] furanyl, thianaphthenyl, indolyl, indolinyl, isoindolyl, isoindolinyl, indolizinyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, benzoxazolyl, 2,3-dihydrobenzoxazolyl, benzo[c]isoxazolyl, benzo[d]isoxazolyl, 2,3-dihydrobenzo[d]isoxazolyl, benzothiazoyl, 2,3-dihydrobenzothiazolyl, benzo[c]isothiazolyl, benzo[d]isothiazolyl, 2,3-dihydrobenzo[d]isothiazolyl, 1H-benzotriazolyl, benzo[c]furanyl, benzo[c][1,2,3]thiadiazolyl, benzo[d][1,2,3]oxadiazolyl, benzo[d][1,2,3]thia-diazolyl, quinolyl, 1,2-dihydroquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolyl 1,2,3,4-tetrahydroisoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 4H-1,4-benzoxazinyl, 2,3-dihydro-4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl or 2,3-dihydro-4H-1,4-benzothiazinyl.

Suitably U represents an indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group.

In an embodiment, the optional substitutents for the carbocyclic or heterocyclic moiety, which may be present at any available position of said moiety, are selected from the group comprising:

$(CH_2)_qS(O)_m$-C_{1-4}alkyl, $(CH_2)_qS(O)_m$-C_{3-6}cycloalkyl, $(CH_2)_qSO_2NR^8R^9$, $(CH_2)_qNR^8R^9$, $(CH_2)_qCO_2R^8$, $(CH_2)_qOR^8$, $(CH_2)_qCONR^8R^9$, $(CH_2)_qNR^8COR^9$, $(CH_2)_qCOR^8$, $(CH_2)_qR^8$, $NR^8SO_2R^9$ and $S(O)_mR^8$,

wherein q is an integer from 0 to 4 inclusive; m is 0,1 or 2;
R^8 and R^9 are independently selected from the group comprising hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, a 5- or 6-membered saturated or unsaturated heterocyclic ring which may be the same or different and which contains one or more heteroatoms which are selected from N, O or $S(O)_m$, with the proviso that the heterocyclic ring does not contain two adjacent O or $S(O)_m$ atoms.

In a further embodiment the optional substitutents for the carbocyclic or heterocyclic moiety are selected from the group comprising morpholine, piperazine, piperidine, pyrrolidine, tetrahydrofuran, dioxolane, oxothiolane and oxides thereof, dithiolane and oxides thereof, dioxane, pyridine, pyrimidine, pyrazine, pyridazine, furan, thiofuran, pyrrole, triazine, imidazole, triazole, tetrazole, pyrazole, oxazole, oxadiazole and thiadiazole.

Other optional substituents for the carbocyclic or heterocyclic moiety and also for other optionally substituted groups include, but are not limited to, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, carboxylate and C_{1-4} alkoxy carboxyl.

In a further embodiment X represents N; A represents a pyridine ring; p is 0; n is 1; and the group R'' is in the 6-position of the pyridopyrimidine ring system.

In a further embodiment X represents N; A represents a pyridine ring; n is 0; p is 1; and the group R^1 is in the 6-position of the pyridopyrimidine ring system.

In a preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate ther of wherein X represents N; Y represents NR^a,

wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring; R'' represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, optionally substituted by one or more R^1 groups selected from halo, C_{1-4} alkyl, carboxy, formyl, hydroxy-C_{1-4} alkyl, 1,3-dioxolan-2-yl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy-C_{1-4} alkanoyl(C_{1-4} alkyl)amino, C_{1-4} alkylamino-C_{1-4} alkyl or di(C_{1-4} alkyl)amino-C_{1-4} alkyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indolyl, benzimidazolyl or indazolyl, more preferably indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

In further preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring, R'' represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, optionally substituted with an R^1 group selected from methylsulphonylethylaminomethyl, methylsulphonylethylamino-carbonyl, methylsulphinylethylamino-methyl, methylsulphinylethylamino-carbonyl, methylsulphonylpropylamino-methyl, methylsulphinylpropylamino-methyl, methylsulphonylpropyamino-carbonyl, methylsulphinylpropylamino-carbonyl, methylsulphonylethyl-(methylamino)-methyl, methylsulphonylethyl-(methylamino)-carbonyl, methylsulphinylethyl-(methylamino)-methyl, methylsulphinylethyl-(methylamino)-carbonyl, methylsulphonylpropyl-(methylamino)-methyl, methylsulphinylpropyl-(methylamino)-methyl, methylsulphonylpropyl-(methylamino)-carbonyl, methylsulphinylpropyl-(methylamino)-carbonyl, methylsulphonamidoethylamino-methyl, methylsulphonamidopropylamino-methyl, sarcosinamidomethyl, glycinylmethyl, glycinamidomethyl, glycinylmethyl methyl ester, acetylaminoethylaminomethyl, piperazinylmethyl, methylpiperazinylmethyl, piperidinylmethyl, N-(prolinamido)methyl, (N,N-dimethyl-prolinamido)methyl, pyridylaminomethyl, cyclopropylaminomethyl, N-(piperidin-4-yl)-N-methylaminomethyl, N,N-dimethylaminoprop-2-ylaminomethyl, N-(2-dimethylaminoethyl)-N-ethylaminomethyl, isopropylacetamido, N-morpholinylacetamido or tetrahydrofuranomethylaminomethyl and optionally further

substituted by one or more C_{1-4} alkyl groups; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indolyl, benzimidazolyl or indazolyl, more preferably indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

In a further preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof, wherein X represents N; Y represents NR^a wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring; n is 0; each R^1 group is selected from hydrogen, halo, C_{1-4} alkyl, carboxy, formyl, hydroxy-C_{1-4} alkyl, 1,3-dioxolan-2-yl, benzyloxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy-C_{1-4} alkanoyl(C_{1-4} alkyl)amino, C_{1-4} alkylamino-C_{1-4} alkyl, di(C_{1-4} alkyl)amino-C_{1-4} alkyl, methylsulphonylethylaminomethyl, methylsulphonylethylamino-carbonyl, methylsulphinylethylamino-methyl, methylsulphinylethylamino-carbonyl, methylsulphonylpropylamino-methyl, methylsulphinylpropylamino-methyl, methylsulphonylpropyamino-carbonyl, methylsulphinylpropylamino-carbonyl, methylsulphonylethyl-(methylamino)-methyl, methylsulphonylethyl-(methylamino)-carbonyl, methylsulphinylethyl-(methylamino)-methyl, methylsulphinylethyl-(methylamino)-carbonyl, methylsulphonylpropyl-(methylamino)-methyl, methylsulphinylpropyl-(methylamino)-methyl, methylsulphonylpropyl-(methylamino)-carbonyl, methylsulphinylpropyl-(methylamino)-carbonyl, methylsulphonamidoethylamino-methyl, methylsulphonamidopropylamino-methyl, sarcosinamidomethyl, glycinylmethyl, glycinamidomethyl, glycinylmethyl methyl ester, acetylaminoethylaminomethyl, piperazinylmethyl, methylpiperazinylmethyl, piperidinylmethyl, N-(prolinamido)methyl, (N,N-dimethyl-prolinamido)methyl, pyridylaminomethyl, cyclopropylaminomethyl, N-(piperidin-4-yl)-N-methylaminomethyl, N,N-dimethylaminoprop-2-ylaminomethyl, N-(2-dimethylaminoethyl)-N-ethylaminomethyl, isopropylacetamido, N-morpholinylacetamido or tetrahydrofuranomethylaminomethyl; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indolyl, benzimidazolyl or indazolyl, more preferably indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

In an especially preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring; R'' represents a furan, imidazole, triazole, oxadiazole, pyrrolidine, piperidine or piperazine ring, optionally substituted by one or more R^1 groups selected from 1,3-dioxolan-2-yl, formyl, carboxy, C_{1-4}-alkyl, prolinamidomethyl, isopropylacetamido, N-morpholinylacetamido, methylsulphonylethylaminomethyl or methylsulphonylethylaminocarbonyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indazolyl, indolyl or benzimidazolyl, more preferably indazolyl; and R^6 represents benzyl, fluorobenzyl, pyridylmethyl or benzenesulphonyl.

In a further especially preferred embodiment of the present invention there is provided a compound of formula (I) or a salt or solvate thereof wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring; n is 0; each R^1 group is selected from hydrogen, halo, benzyloxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino or hydroxy-C_{1-4} alkanoyl(C_{1-4} alkyl)amino, more preferably dimethylamino; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indazolyl, indolyl or benzimidazolyl, more preferably indazolyl; and R^6 represents benzyl, fluorobenzyl, pyridylmethyl or benzenesulphonyl.

Preferred compounds of the present invention include:
(1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N4-(1-Benzyl-1H-indazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
(1-Benzyl-1H-indazol-5-yl)-6-(N-(2-hydroxyethyl)-N-methylamino)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(pyrido[3,4-d]pyrimidin-4-yl)-amine;
(2-Benzyl-1H-benzimidazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N4-(1-Benzyl-1H-indol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(2-Benzyl-1H-benzimidazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]-pyrimidine-4,6-diamine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-[1,3-dioxolan-2-yl]-furan-2-yl)-pyrido[3,4-d]-pyrimidin-4-yl)-amine;
5-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;

(2S)-1-(5-(4-(1-Benzyl-1H-indazol-5-ylamino)-6-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-3H-imidazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N6,N6-Dimethyl-N4-(1-pyridin-2-ylmethyl-1H-indazol-5-yl)-pyrido[3,4-d]pyrimidine-4,6-diamine;
N6,N6-Dimethyl-N4-(1-pyridin-3-ylmethyl-1H-indazol-5-yl)-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-Benzyl-3-methyl-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-(2-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-(4-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-Benzenesulphonyl-1H-indol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(3-Benzenesulphonyl-1H-indol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
(1-Benzyl-1H-indazol-5-yl)-(6-imidazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,4-triazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,3-triazol-2-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,3-triazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-pyrrolidin-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-piperidin-1-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N4-(1-Benzyl-1H-indazol-5-yl)-N6-ethyl-N6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
2-(4-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-piperazin-1-yl)-N-isopropyl-acetamide;
2-(4-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-piperazin-1-yl)-1-morpholin-4-yl-ethanone;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(4-methyl-piperazin-1-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazolyl-5-yl)-(6-benzyloxy-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesuphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido-[3,4-d]pyrimidin-4-yl)-amine;
5-[4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido-[3,4-d]pyrimidin-6-yl]-furan-2-carboxylic acid;
5-[4-(1-benzyl-1H-indazol-5-ylamino)-pyrido-[3,4-d]pyrimidin-6-yl]-furan-2-carboxylic acid 2-methanesulphonyl-ethylamide;
*N*4-(1-Benzyl-1H-indazol-5-yl)-*N*6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine; N4-[1-(4-Hydroxybenzyl)-1H-indazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Other preferred compounds of the present invention include:
N4-[1-(*S*,*R*-α-Methylbenzyl)-1H-indazol-5-yl]-*N*6,*N*6-dimethyl-pyrido-[3,4-d]pyrimidin-4,6-diamine;
N4-(3-Benzylsulphonyl-1H-indazol-6-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]-pyrimidine-4,6-diamine;
N4-(3-Benzyl-1H-indazol-6-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]-pyrimidine-4,6-diamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Particularly preferred compounds of the present invention include:
N4-(1-Benzyl-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-Benzyl-1H-indazol-5-yl)-N6-ethyl-N6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesuphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido-[3,4-d]pyrimidin-4-yl)-amine;
N4-(1-Benzyl-1H-indazol-5-yl)-N6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine;

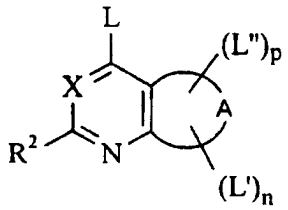
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen in the compound of formula (I). The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance although for therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) the reaction of a compound of formula (II)

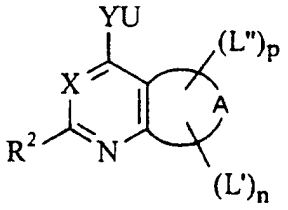


(II)

wherein A, X, n, p and R^2 are as defined above and L, L' and L" are suitable leaving groups, with a compound of formula (III)

UYH (III)

wherein U and Y are as defined above, to prepare a compound of formula (IV)

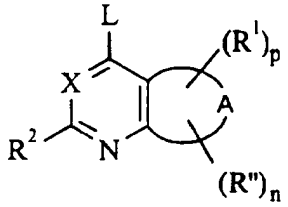


(IV)

and subsequently (b) where n is 1, reaction with an appropriate reagent to substitute the group R'' onto the ring A by replacement of the leaving group L'; and (c) where p is other than 0, reaction with appropriate reagent(s) to substitute the group(s) R^1 onto the ring A by replacement of the leaving group(s) L''; and, if desired, (d) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

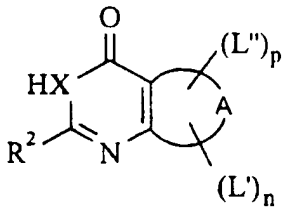
Alternatively, the compound of formula (II) as defined above is reacted with the appropriate reagents to substitute the groups R'' and R^1 onto the ring A by replacement of the respective leaving groups and then the product thereby obtained (of formula (V) below) is reacted with the compound of formula (III) as defined above, followed, if desired, by conversion of the compound of formula (I) thereby obtained into another compound of formula (I).

In a variant of this alternative the compound of formula (V)



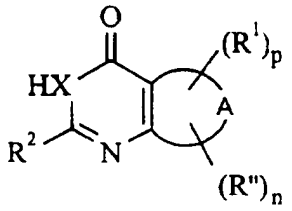
(V)

may be prepared by the reaction of a compound of formula (VI)



(VI)

with appropriate reagents to substitute the group(s) R^1 and the group R'' onto the ring A to prepare a compound of formula (VII)



(VII)

and subsequent reaction to incorporate the leaving group L. For example, a chloro leaving group can be incorporated by reaction of a corresponding 3,4-dihydropyrimidone with carbon tetrachloride/triphenylphosphine in an appropriate solvent.

Simplified versions of these general processes will apply where either (i) p is 0 and n is 1 or (ii) where n is 0 and p is other than 0.

The group R'' may, therefore, be substituted onto the ring A by replacement of a suitable leaving group. This is especially suitable for preparing compounds where R'' is a substituted or unsubstituted phenyl or heterocyclic ring system; such compounds may, for example, be prepared by reaction of the corresponding aryl or heteroaryl stannane derivative with the corresponding compound of formula (IV) carrying the leaving group L' in the appropriate position on the ring.

The group(s) R^1 may, therefore, also be substituted onto the ring A by replacement of suitable leaving group(s). This is especially suitable for preparing compounds of formula (I) wherein an R^1 group is linked to the ring A by a nitrogen atom; such compounds may, for example, be obtained by reaction of the amine corresponding to the group R^1 with the corresponding compound carrying a halo substituent in the appropriate position on the ring A.

The reagents used to effect the substitution of the groups R'' and R^1 onto the ring A may, in certain circumstances, include appropriate protecting group(s) well known to the person skilled in the art for particular functionalities. This may, for example, be suitable where either of the groups R'' or R^1 contain a free amino functionality. Such protecting group(s) would be removed by standard methods after the substitution onto the ring A has been effected. For a description of protecting groups and their use see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd edn., John Wiley & Sons, New York, 1991.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) reacting a compound of formula (IV) as defined above with appropriate reagent(s) to prepare a compound wherein either the group L' (when n=1) or the group(s) L'' (when p is other than 0) is(are) replaced with an appropriately functionalised group Z;

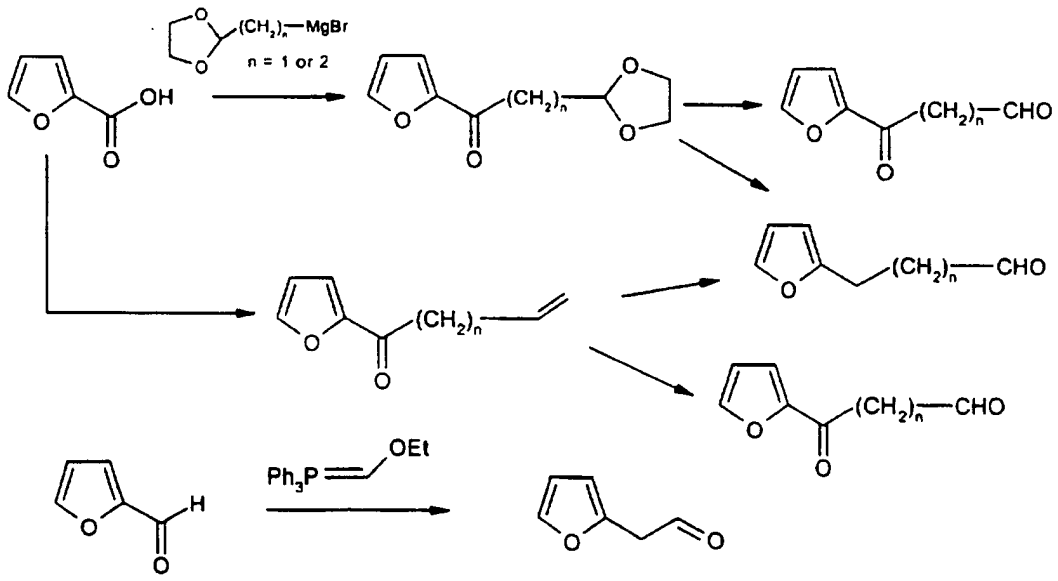
and (b) subsequently converting the group Z into the group R'' where L' has been replaced or into the group R^1 where L'' has been replaced by means of appropriate reagent(s); (c) reacting with appropriate reagents to substitute the other of R^1 and R'' onto the ring A by replacement of the remaining leaving group L'' and L' respectively, if present; and, if desired, (d) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

Such processes are particularly suitable for the preparation of compounds of formula (I) wherein either R'' carries or R^1 represents a substituent selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents NR^{12}. In such cases preferably the group Z carries a terminal formyl group (CHO).

Such processes are especially suitable for the preparation of compounds of formula (I) wherein either (i) p is 0, n is 1 and R'' carries a substituent selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents NR^{12}, or (ii) p is 1, n is 0 and R^1 is selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents NR^{12}.

Where Z carries a formyl group the compound may be suitably prepared from the corresponding dioxolanyl substituted compound, for example by acid hydrolysis. The dioxolanyl substituted compound may be prepared by reaction of a compound of formula (IV) with an appropriate reagent to substitute the relevant leaving group with the substituent carrying the dioxolanyl ring. This reagent could, for example, be an appropriate heteroaryl stannane derivative.

Where Z carries a terminal formyl group the compound could suitably be prepared by reaction of a compound of formula (IV) with an appropriate heteroaryl stannane derivative. This derivative is either readily available or can be readily synthesised by those skilled in the art using conventional methods of organic synthesis. Suitable possibilities for preparation of compounds where R'' carries the aforementioned substituents include the following schematic examples:-



The resulting compounds would, for example, then be converted into the respective stannane derivative.

Analogous methods could be used for phenyl and other heterocyclic ring systems and also for the preparation of compounds where R^1 represents one of the aforementioned substituents.

Therefore a suitable process may comprise reaction of the compound in which the group Z carries a terminal formyl group (i.e. a -CHO or -(C_{1-3} alkylene)-CHO group) with a compound of formula HM^2-M^3-M^4, a compound of formula HM^2-$M^{3'}$-M^6 or a compound of formula HM^5, wherein M^2 represents NR^{12}. The reaction preferably involves a reductive amination by means of an appropriate reducing agent, for example sodium triacetoxyborohydride.

A similar process would be involved where in M^1 one CH_2 group was replaced with a CO group and M^2 was NR^{12}. If necessary, in certain circumstances, the ketone could be protected by standard methods to ensure that the reductive amination involved the aldehyde functionality.

For the preparation of those compounds wherein in M^1 the CH_2 group adjacent to M^2 is replaced with a CO group a suitable process would comprise reaction of a compound in which the group Z carries a -(C_{0-3} alkylene)-CO_2H group with a compound of formula HM^2-M^3-M^4, a compound of formula HM^2-$M^{3'}$-M^6 or a compound of formula HM^5 , wherein M^2 represents NR^{12}.

Alternatively, an analogous scheme to those described above could be used wherein the substitution of the groups R'' and R^1 onto the ring A occurs prior to the coupling reaction with the compound of formula (III).

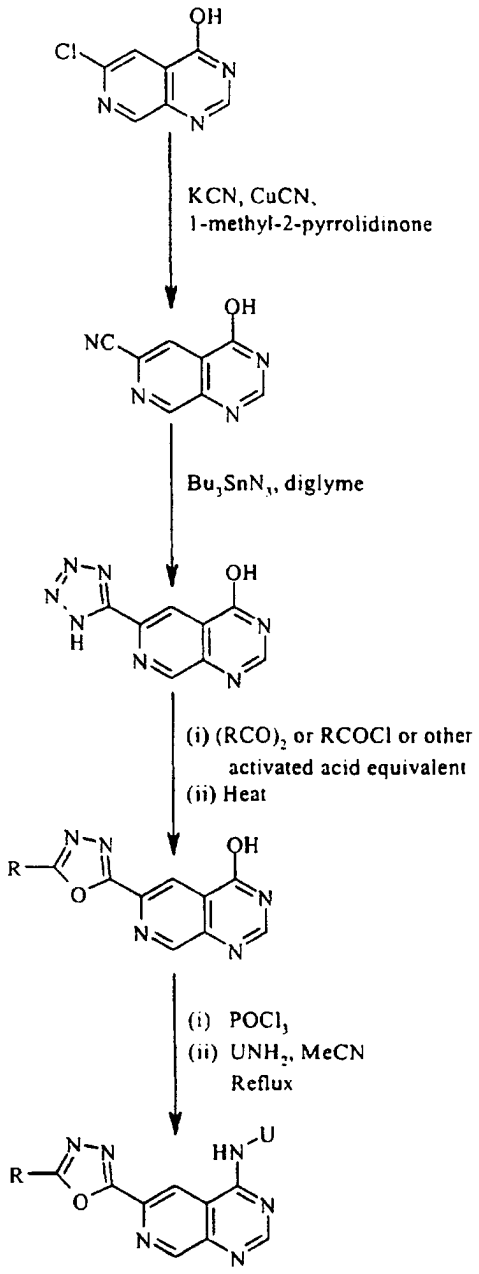
According to a further alternative process the group Z is converted into the group R'' by a *de novo* synthesis of a substituted or unsubstituted heterocyclic ring system using appropriate reagents. Such a process would involve standard synthetic methodology known to the person skilled in the art for building up the heterocyclic ring system.

For example, Z could suitably represent an alkyne group which when reacted with an appropriate nitrile oxide results in the formation of an isoxazole ring system; reaction with an azide would result in the formation of a triazole ring system. The group Z could also suitably represent an amidoxime group (derived from a cyano group) which when reacted with an activated carboxylic acid derivative (such as an acid chloride or an acid imidazolide) would result in the formation of a 1,2,4-oxadiazole ring system. The group Z could also suitably repres nt a

bromomethylenecarbonyl group which would be reacted with an imidate to result in the formation of an oxazole ring system, with a guanidino group to result in the formation of an N-imidazole ring system or with an amidine group to result in the formation of a C-imidazole ring system. The group Z could also suitably represent an activated carboxylic acid group which would be reacted to form a hydrazinoketone which would subsequently be reacted with another activated carboxylic acid derivative to result in the preparation of a 1,3,4-oxadiazole ring system. Thus reaction of a compound carrying a relevant Z group with appropriate reagents carrying one of
-C=N=O, -NH-C(NH_2)=NH, -COX, -C(NH_2)=NOH, -C(OMe)=NH, or
-C(NH_2)=NH as a terminal group would result in the formation of the ring systems indicated above.

Alternatively, an analogous scheme to those described above could be used wherein the substitution of the group R'' onto the ring A occurs prior to the coupling reaction with the compound of formula (III).

The following scheme outlines, for example, the synthesis of derivatives carrying a substituted 1,3,4-oxadiazole ring as an R'' substituent:



Such processes are particularly suitable for the preparation of the compounds of formula (I) wherein R" carries a substituent selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents $CR^{12}R^{13}$, including those in which in M^1 one CH_2 group is replaced by a CO group.

Such processes are especially suitable for the preparation of compounds of formula (I) wherein either (i) p is 0, n is 1 and R'' carries a substituent selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents $CR^{12}R^{13}$, or (ii) p is 1, n is 0 and R^1 is selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined above in which M^2 represents $CR^{12}R^{13}$.

Suitable leaving groups for L, L' and L'' will be well known to those skilled in the art and include, for example, halo such as chloro and bromo; sulphonyloxy groups such as methanesulphonyloxy and toluene-p-sulphonyloxy; alkoxy groups; and triflate.

The coupling reaction referred to above with the compound of formula (III) is conveniently carried out in the presence of a suitable inert solvent, for example a C_{1-4} alkanol, such as isopropanol, a halogenated hydrocarbon, an ether, an aromatic hydrocarbon or a dipolar aprotic solvent such as acetone or acetonitrile at a non-extreme temperature, for example from 0 to 150°, suitably 10 to 100°C, preferably 50 to 100°C.

Optionally, the reaction is carried out in the presence of a base when Y = NH. Examples of suitable bases include an organic amine such as triethylamine, or an alkaline earth metal carbonate, hydride or hydroxide, such as sodium or potassium carbonate, hydride or hydroxide. When YH = OH or SH it is necessary to perform the reaction in the presence of a base, and in such a case the product is not obtained as the salt.

The compound of formula (I) in the case in which Y = NR^b may be obtained from this process in the form of a salt with the acid HL, wherein L is as hereinbefore defined, or as the free base by treating the salt with a base as hereinbefore defined.

The compounds of formulae (II) and (III) as defined above, the reagents to substitute the group(s) R^1 and the group R'', and the reagent(s) to convert the group Z into the group R^1 or R'' are either readily available or can be readily synthesised by those skilled in the art using conventional methods of organic synthesis.

As indicated above, the compound of formula (I) prepared may be converted to another compound of formula (I) by chemical transformation of the appropriate

substituent or substituents using appropriate chemical methods (see for example, J.March "Advanced Organic Chemistry", Edition III, Wiley Interscience, 1985).

For example, a group R^1 may be substituted onto the ring A by replacement of another group R^1 which is a suitable leaving group. This is especially suitable for preparing compounds of formula (I) wherein an R^1 group is linked to the ring A by a nitrogen atom; such compounds may, for example, be obtained by reaction of the amine corresponding to the group R^1 with the corresponding compound of formula (I) carrying a halo substituent in the appropriate position on the ring A.

Similarly a group R" may be substituted onto the ring A by replacement of a group R^1 which is a suitable leaving group. This is especially suitable for preparing compounds where R" is a phenyl or heterocyclic ring system; such compounds may, for example, be prepared by reaction of the corresponding aryl or heteroaryl stannane derivative with the corresponding compound of formula (I) carrying a halo substituent in the appropriate position on the ring A.

For example, a compound containing an alkyl or aryl mercapto group may be oxidised to the corresponding sulphinyl or sulphonyl compound by use of an organic peroxide (e.g. benzoyl peroxide) or suitable inorganic oxidant (eg OXONE ®).

A compound containing a nitro substituent may be reduced to the corresponding amino-compound, e.g. by use of hydrogen and an appropriate catalyst (if there are no other susceptible groups) or by use of Raney Nickel and hydrazine hydrate.

Amino or hydroxy substituents may be acylated by use of an acid chloride or an anhydride under appropriate conditions. Equally an acetate or amide group may be cleaved to the hydroxy or amino compound respectively by treatment with, for example, dilute aqueous base.

In addition reaction of an amino substituent with triphosgene and another amine (eg aqueous ammonia, dimethylamine) gives the urea substituted product.

An amino substituent may also be converted to a dimethylamino substituent by reaction with formic acid and sodium cyanoborohydride.

A formyl substituent may be converted to a hydroxymethyl or a carboxy substituent by standard reduction or oxidation methods respectively.

All of the above-mentioned chemical transformations may also be used to convert one compound of formula (II) to a further compound of formula (II) prior to any subsequent reaction; or to convert one compound of formula (II) to a further compound of formula (III) prior to any subsequent reaction.

Various intermediate compounds used in the above-mentioned processes, including but not limited to certain of the compounds of formulae (II), (III), (IV), (V), (VI) and (VII) as illustrated above, are novel and thus represent a further aspect of the present invention.

The compounds of formula (I) and salts thereof have anticancer activity as demonstrated hereinafter by their inhibition of the protein tyrosine kinase c-erbB-2, c-erbB-4 and/or EGF-r enzymes and their effect on selected cell lines whose growth is dependent on c-erbB-2 or EGF-r tyrosine kinase activity.

The present invention thus also provides compounds of formula (I) and pharmaceutically acceptable salts or solvates thereof for use in medical therapy, and particularly in the treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds of the present invention are especially useful for the treatment of disorders caused by aberrant c-erbB-2 and/or EGF-r activity such as breast, ovarian, gastric, pancreatic, non-small cell lung, bladder, head and neck cancers, and psoriasis.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity, including susceptible malignancies, which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in therapy.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of cancer and malignant tumours.

A further aspect of the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of psoriasis.

Whilst it is possible for the compounds, salts or solvates of the present invention to be administered as the new chemical, it is preferred to present them in the form of a pharmaceutical formulation.

According to a further feature of the present invention there is provided a pharmaceutical formulation comprising at least one compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain for example 0.5mg to 1g, preferably 70mg to 700mg, more preferably 5mg to 100mg of a compound of the formula (I) depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The animal requiring treatment with a compound, salt or solvate of the present invention is usually a mammal, such as a human being.

A therapeutically effective amount of a compound, salt or solvate of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or vet rinarian. However, an effective amount of a compound of the present invention for the treatment of neoplastic

growth, for example colon or breast carcinoma will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate of the present invention may be determined as a proportion of the effective amount of the compound per se.

The compounds of the present invention and their salts and solvates may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in anti-cancer therapy, combination with other chemotherapeutic, hormonal or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Certain embodiments of the present invention will now be illustrated by way of example only. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

^{1}H NMR spectra were obtained at 500MHz on a Bruker AMX500 spectrophotometer, on a Bruker spectrophotometer at 300Mz, or on a Bruker AC250 or Bruker AM250 spectrophotometer at 250MHz. J values are given in Hz. Mass spectra were obtained on one of the following machines: VG Micromass Platform (electrospray positive or negative), HP5989A Engine (thermospray positive) or Finnigan-MAT LCQ (ion trap) mass spectrometer. Analytical thin layer chromatography (tlc) was used to verify the purity of some intermediates which could not be isolated or which were too unstable for full characterisation, and to follow the progess of reactions. Unless

otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254). Unless otherwise stated, column chromatography for the purification of some compounds used Merck Silica gel 60 (Art. 1.09385, 230-400 mesh), and the stated solvent system under pressure.

Petrol refers to petroleum ether, either the fraction boiling at 40-60°C, or at 60-80°C.
Ether refers to diethylether.
DMAP refers to 4-dimethylaminopyridine.
DMF refers to dimethylformamide.
DMSO refers to dimethylsulphoxide.
THF refers to tetrahydrofuran.
TMEDA refers to *N,N,N',N'*-tetramethylethylenediamine.
TFA refers to trifluoroacetic acid.
HPLC refers to high pressure liquid chromatography.
RT refers to retention time.

Useful preparative techniques are described in WO96/09294, WO97/03069 and WO97/13771; also described in these publications are appropriate intermediate compounds other than those detailed below.

General Procedures

(A) Reaction of an amine with a bicyclic species containing a 4-chloropyrimidine ring

The optionally substituted bicyclic species and the specified amine were mixed in an appropriate solvent (acetonitrile unless otherwise specified), and heated to reflux. When the reaction was complete (as judged by tlc), the reaction mixture was allowed to cool. The resulting suspension was diluted, *e.g.* with acetone, and the solid collected by filtration, washing *e.g.* with excess acetone, and dried at 60°C *in vacuo*, giving the product as the hydrochloride salt. If the free base was required (*e.g.* for further reaction), this was obtained by treatment with a base *e.g.* triethylamine; purification by chromatography was then performed, if required.

(B) Reaction of a product from Procedure (A) with a heteroaryl tin reagent

A stirred mixture of the product from Procedure (A), (containing a suitable leaving group such as chloro, bromo, iodo or triflate), a heteroaryl stannane and

a suitable palladium catalyst, such as bis-(triphenylphosphine)palladium (II) chloride or 1,4-bis(diphenylphosphino)-butane palladium (II) chloride (prepared as described in C.E. Housecroft et. al., Inorg. Chem., (1991), 30(1), 125-130), together with other appropriate additives, were heated at reflux in dry dioxane or another suitable solvent under nitrogen until the reaction was complete. The resulting mixture was generally purified by chromatography on silica.

(C) Reaction of the product from Procedure (A) with a second amine

The product of Procedure (A) (containing a suitable leaving group such as chloro) was dissolved in an excess of the desired amine (or a solution thereof) and heated in a pressure vessel (*e.g.* at 130°C for 17hr). The cooled mixture was generally purified by chromatography on silica.

Preparation Of Intermediates

1-Benzyl-5-nitro-1H-indole

Dry dimethylsulphoxide (20 ml) was added to potassium hydroxide (4.2 g, 0.074 mol) (crushed pellets) and the mixture was stirred under nitrogen for 5 mins. 5-Nitroindole (commercially available) (3.0 g, 0.019 mol) was then added and the red mixture stirred for 30 min at room temperature. The mixture was then cooled to -10 °C, benzyl bromide (4.4 ml, 0.037 mol) was slowly added and the mixture stirred and allowed to warm to room temperature over a period of 40 mins. Water (50 ml) was then added and the mixture was extracted with diethyl ether (2 x 200 ml). The extracts were washed with water (4 x 50 ml), dried over sodium sulphate and evaporated to leave an oily solid. The excess benzyl bromide was removed by dissolving the whole in diethyl ether (50 ml), diluting this solution with 40-60 petrol (50 ml) and then gradually removing the diethyl ether *in vacuo* to leave a yellow solid suspended in the petrol. The solid was filtered, washed with copious amounts of 40-60 petrol and dried to give 1-benzyl-5-nitroindole (2.4 g, 51%) as a yellow solid, m.p. 102-104 °C; δH [$^2H_6$]-DMSO 8.53 (1H, s, 4-H), 8.00 (1H, d, J 9, 6-H), 7.78 (1H, s, 2-H), 7.68 (1H, d, J 9, 7-H), 7.36-7.20 (5H, m, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 6.81 (1H, s, 3-H), 5.52 (2H, s, CH_2).

5-Amino-1-benzyl-1H-indole

A solution of 1-benzyl-5-nitroindole (0.51 g, 0.02 mol) in a mixture of ethyl acetate (25 ml) and methanol (25 ml) was carefully added to 10% palladium on charcoal (45 mg). The resulting suspension was stirred at room temperature under an atmosphere of hydrogen. When the reaction was complete (indicated by tlc or calculated uptake of hydrogen) the suspension was filtered through a pad of Hyflo™, and the filtrate evaporated to dryness to give 5-amino-1-benzylindole (0.40 g, 91%) as an off-white solid; m.p. 66-68 °C; δH [$^2H_6$]-DMSO 7.30-7.12 (6H, m, 2-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 7.08 (1H, d, J 8, 7-H), 6.70 (1H, s, 4-H), 6.49 (1H, d, J 8, 6-H), 6.18 (1H, s, 3-H), 5.28 (2H, s, CH_2), 4.38 (2H, br s, NH_2).

2-Benzyl-5-nitro-1H-benzimidazole

A mixture of 4-nitro-o-phenylene diamine (1.54g) and phenylacetic acid (2.04g) in 5N aqueous HCl (16ml) were heated at 110 °C under nitrogen for 22 hours. The mixture was cooled to room temperature and the accumulated black solid collected by filtration. This crude residue was then adsorbed onto silica and chromatographed to give the title compound (0.84g) as a purple foam; δH $CDCl_3$ 9.70 (1H, bs), 8.15 (1H, d), 7.30 (7H, m), 4.30 (2H,s); m/z $(M + 1)^+$ 254.

5-Amino-2-benzyl-1H-benzimidazole

The title compound was prepared from 5-nitro-2-benzylbenzimidazole by an analogous reduction method to that described above for 5-amino-1-benzyl-1H-indole; m/z $(M + 1)^+$ 224. Also note the published method (J. Het. Chem., 23, 1109-13, (1986)).

1-*N*-Benzyl-5-nitro-1H-indazole and 2-*N*-Benzyl-5-nitro-1H-indazole

A stirred mixture of 5-nitroindazole (50g), potassium carbonate (46.6g, 1.1 equiv.) and benzyl bromide (57.6g, 1.1 equiv) in *N,N*-dimethylformamide (500 ml) was heated at 75°C for a period of 4 hours. The reaction was then cooled and water (500ml) was gradually added to precipitate the product which was filtered off and washed with water (50ml) and dried in the air at ambient temperature. The weight of pale yellow solid thus obtained was 72.3g (93%), m.pt. 95-97°C; HPLC (Partisil 5, dichloromethane, 4ml/min, 250nm) gave an isomer ratio (1-*N*-benzyl : 2-*N*-benzyl) of 63:37 (RT-1*N* 3.4min, RT-2*N* 6.6min). To a filtered solution of the mixed

regioisomers (100g) in acetone (470ml) at room temperature was added, gradually with stirring, water (156ml) and the mixture was stirred for one hour. The resultant yellow crystalline solid was filtered off and dried in the air at ambient temperature to give 36.4g (34%) of material; m.pt.124-126^{0}C; HPLC showed an isomer ratio (1-*N*-benzyl : 2-*N*-benzyl) of 96:4; δH ($CDCl_3$) 5.58 (2H,s,CH_2), 7.12-7.15(2H) & 7.22-7.29(3H)-(phenyl), 7.33(1H,dt, J=1Hz & 9Hz, H-7), 8.15(1H,dd, J=2Hz & 9Hz,H-6), 8.19(1H,d,J=1Hz,H-3), 8.67 (1H,dd,J=1Hz & 2Hz, H-4).

Also note the published method in FR 5600, 8 January 1968.

5-Amino-1-*N*-benzyl-1H-indazole

1-Benzyl-5-nitroindazole (400g) was suspended in ethanol (5 litre) and hydrogenated in the presence of 5% platinum on carbon catalyst (20g) operating at 1 bar pressure and 50-60^{0}C. When hydrogen uptake was complete the reactor contents were heated to 70^{0}C, discharged and filtered while still hot and the filtrate concentrated to ~4 litre which caused some crystallisation. Water (4 litre) was then gradually added with stirring and the mixture was stirred at 5^{0}C overnight. The resultant crystals were filtered off and air-dried at ambient temperature to give 305g (86%) of material, m.pt.150-152^{0}C; HPLC (Supelcosil ABZ +, gradient 0.05% trifluoroacetic acid in water/0.05% trifluoroacetic acid in acetonitrile,1.5ml/min, 220nm) showed <1% of the corresponding 2-*N*-isomer (RT-1*N* 6.03min, RT-2*N* 5.29min); δH ($CDCl_3$) 3.3-3.8(2H,broad s,NH_2), 5.47 (2H,s,CH_2), 6.74(1H,dd,J=2Hz & 9Hz,H-6), 6.87(1H,dd,J=1Hz & 2Hz,H-4), 7.06-7.11(3H) & 7.17-7.25(3H)-(phenyl & H-7), 7.77(1H,d,J=1Hz,H-3).

Also note the published method in FR 5600, 8 January 1968.

1-Benzyl-3-methyl-5-nitro-1H-indazole

2-Fluoro-5-nitroacetophenone (H. Sato et al, Bioorganic and Medicinal Chemistry Letters, 5(3), 233-236, 1995) (0.24g) was treated with triethylamine (0.73ml)and benzyl hydrazine dihydrochloride (0.255g) in ethanol (20ml) at reflux under N_2 for 8 days. The mixture was cooled and the solid 1-benzyl-3-methyl-5-nitroindazole (0.16g) was collected by filtration; m/z $(M+1)^+$ 268.

1-Benzyl-3-methyl-1H-indazol-5-ylamine

1-Benzyl-3-methyl-5-nitroindazole (0.15g) in THF (15ml) was treated with platinum on carbon (0.05g, 5%) under an atmosphere of hydrogen at room temperature. When hydrogen uptake was complete, the mixture was filtered and concentrated *in vacuo* to give the title compound; m/z $(M+1)^+$ 268.

Further amino-indazole intermediates

The relevant nitro-substituted 1H-indazole was treated with a base such as potassium carbonate or sodium hydroxide in a suitable solvent, such as acetone or acetonitrile. The appropriate aryl halide or heteroaryl halide was added and the reaction mixture heated or stirred at room temperature overnight. Subsequent concentration *in vacuo* and chromatography on silica gave the desired 1-substituted nitro-1H-indazoles. Hydrogenation was carried out by analogy with the preparation of 5-amino-1-benzyl-1H-indole described above.

Amines prepared by such methods and specifically used in the preparation of the later Examples include:-

5-Amino-1-benzyl-1H-indazole; m/z $(M+1)^+$ 224

5-Amino-1-(2-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 242

5-Amino-1-(3-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 242

5-Amino-1-(4-fluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 242

5-Amino-1-(2-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$ 225

5-Amino-1-(3-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$ 225

5-Amino-1-(2,3-difluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 260

5-Amino-1-(3,5-difluorobenzyl)-1H-indazole; m/z $(M+1)^+$ 260.

Other amines prepared by such methods include:

5-Amino-1-(4-pyridylmethyl)-1H-indazole; m/z $(M+1)^+$ 225.

1-Benzenesulphonylindol-5-yl-amine was prepared according to the published method (J. Org. Chem., 55, 1379-90, (1990)).

3-Benzenesulphonylindol-6-yl-amine

3-Benzenesulphonyl-6-nitroindole (K. Wojciechowski and M Makosza, Tet. Lett., 25 (42), p4793, 1984) was hydrogenated by analogy with the procedures above

to give the title compound; δH [$^2H_6$]DMSO 11.64 (1H,s), 7.94 (2H,m), 7.81 (1H,s), 7.57 (3H,m), 7.49(1H,d), 6.60(1H,s), 6.55 (1H,dd), 5.40 (2H,s).

N-5-[*N*-*tert*-Butoxycarbonyl)amino]-2-chloropyridine

A stirred solution of 6-chloronicotinic acid (47.3g), diphenylphosphoryl azide (89.6g) and triethylamine (46ml) in t-butanol (240ml) were heated under reflux under nitrogen for 2.5 hours. The solution was cooled and concentrated *in vacuo*. The syrupy residue was poured into 3 litres of a rapidly stirred solution of 0.33N aqueous sodium carbonate. The precipitate was stirred for one hour and filtered. The solid was washed with water and dried *in vacuo* at 70°C to give the title compound (62g) as a pale brown solid; m.p. 144-146°C; δH [$^2H_6$]-DMSO 8.25(1H,d), 7.95 (1H, bd), 7.25 (1H, d), 6.65(1H, bs), 1.51 (9H,s); m/z $(M + 1)^+$ 229.

This material may subsequently be carried forward to the appropriately substituted pyridopyrimidine intermediate according to the procedures as described in WO95/19774, J. Med. Chem., 1996, 39, pp 1823-1835, and J. Chem. Soc., Perkin Trans. 1, 1996, pp 2221-2226. Specific compounds made by such procedures include 6-chloro-pyrido[3,4-d]pyrimidin-one and 4,6-dichloro-pyrido[3,4-d]pyrimidine.

2-*N*,*N*-Dimethylamino-4-nitropyridine

2-Chloro-4-nitropyridine (0.64g) was treated with aqueous dimethylamine (10ml, 25%) at reflux for 30 minutes. The mixture was diluted with water and filtered. The solid was washed with water and dried *in vacuo* to give the title compound (0.67g); δH [$^2H_6$]DMSO 9.05 (1H,d), 8.30(1H,dd), 6.84(1H,d), 3.28 (6H,s).

2-*N*,*N*-Dimethylamino-4-aminopyridine

2-*N*,*N*-Dimethylamino-4-nitropyridine (0.67g) in ethanol (50ml) was added to 10% palladium on charcoal and stirred under an atmosphere of hydrogen. When the reaction was complete, the suspension was filtered through a pad of Hyflo™ and the filtrate concentrated *in vacuo* to give the title compound (0.49g); δH [$^2H_6$]DMSO 7.57 (1H,d), 6.88(1H,dd), 6.41(1H,d), 4.39(2H,bs), 3.80 (6H,s); m/z ($M+1^+$) 138.

N-(4-*N'*,*N'*-Dimethylaminopyrid-3-yl)-2,2-dimethylpropionamide

2-*N*,*N*-Dimethylamino-4-aminopyridine (1.37g) in methylene chloride (20ml) under N_2 was treated with triethylamine (1.53ml) and pivaloyl chloride (1.32g) over 5 minutes. After 16 hours at room temperature, the mixture was diluted with methylene chloride, washed with water, dried and concentrated to give the title compound (2.2g); δH [$^2H_6$]DMSO 9.20(1H,s), 8.22 (1H,d), 7.70(1H,dd), 6.60(1H,d), 2.98(6H,s), 1.20 (9H,s); m/z ($M+1^+$) 222.

2-(*N*,*N*-Dimethylamino)-5-(2,2-dimethylpropionamido)-pyridine-4-carboxylic acid

N-(4-*N'*,*N'*-Dimethylaminopyrid-3-yl)-2,2-dimethylpropionamide (1.1g) in dry THF under N_2 at -70°C was treated with TMEDA (1.45g) and butyl lithium (1.6M, 8ml). The mixture was warmed to 0°C for three hours before being recooled to -70°C. Carbon dioxide was bubbled through the solution for 1 hour and the resulting solution was warmed to room temperature under a carbon dioxide atmosphere and stirred there for 16 hours. The resulting mixture was concentrated *in vacuo* and partitioned between ether and water. The aqueous layer was concentrated *in vacuo* to give the title compound (1.0g); δH [$^2H_6$]DMSO 13.50(1H,s), 9.22(1H,s), 7.26(1H,s), 2.95(6H,s), 1.20 (9H,s); m/z ($M+1^+$) 266.

5-Amino-2-(*N*,*N*-dimethylamino)-pyridine-4-carboxylic acid

2-(*N*,*N*-Dimethylamino)-5-(2,2-dimethylpropionamido)-pyridine-4-carboxylic acid (0.8g) was treated with 5N HCl at reflux for 5 hours. The mixture was allowed to cool and evaporated to dryness to give the title compound (0.54g); δH [$^2H_6$]DMSO 8.15(1H,s), 7.35(2H,bs), 6.70(1H,s), 3.10(6H,s); m/z ($M+1^+$) 182.

6-(N,N-Dimethylamino)-pyrido[3,4-d]pyrimidin-4-one

5-Amino-2-(*N*,*N*-dimethylamino)-pyridine-4-carboxylic acid (0.54g) was treated with formamidine acetate (3.12g) in glacial acetic acid (20ml) and heated at reflux for 16 hours. The mixture was cooled, evaporated to dryness *in vacuo* and partitioned between ethyl acetate and water. The organic phase was separated, dried over magnesium sulphate and concentrated *in vacuo* to give, after chromatography on silica, the title compound (0.25g); δH $CDCl_3$ 9.10(1H,d), 8.80(1H,s), 8.31(1H,s), 7.07(1H,s), 3.20(6H,s); m/z ($M+1^+$) 191.

Alternatively, 6-chloro-pyrido[3,4-d]pyrimidin-4-one (26.14g) was treated with 2N dimethylamine in ethanol (200ml) and heated at 130°C in a Parr bomb for 3 days. The cooled mixture was filtered and triturated from isopropanol to give the title compound (16.61g) as a yellow solid; m/z ($M+1^+$) 191.

4-Chloro-6-(*N,N*-dimethylamino)-pyrido[3,4-d]pyrimidine

6-(*N,N*-Dimethylamino)-pyrido[3,4-d]pyrimidin-4-one (12g) was carefully treated with phosphorus oxychloride (42ml) and triethylamine (18ml) at room temperature under N_2. After 1 hour at room temperature and 1 hour at 50°C, the mixture was concentrated *in vacuo*, azeotroping with toluene, then taken up in ethyl acetate, washed with sodium bicarbonate solution, dried and concentrated *in vacuo* to give the title compound (10.34g); δH $CDCl_3$ 9.13(1H,s), 8.74(1H,s), 6.69(1H,s), 3.25(6H,s).

6-Cyano-pyrido[3,4-d]pyrimidin-4-one

6-Chloro-pyrido[3,4-d]pyrimidin-4-one (10g) in 1-methyl-2-pyrrolidinone (100ml) was treated with copper (I) iodide (10.52g) and potassium cyanide (7.10g) at 215°c for 72 hours under N_2. Further potassium cyanide was added (3.58g) and heating continued at 230°C for 70 hours. The 1-methyl-2-pyrrolidinone was removed by distillation at reduced pressure and the residue absorbed onto silica. Chromatography gave the title compound (2.4g) as a beige solid; δH [$^2H_6$]DMSO 13.0(1H,bs), 9.25 (1H,s), 8.55 (1H,s), 8.50 (1H,s); m/z ($M-1^+$) 171.

6-(1,2,3,4-Tetrazol-5-yl)-pyrido[3,4-d]pyrimidin-4-one

6-Cyano-pyrido[3,4-d]pyrimidin-4-one (0.3g) in diglyme (2ml) was treated with tributyl tin azide (0.49g) at reflux under N_2 for 15 hours. The cooled mixture was partitioned between ethyl acetate and water and the aqueous phase extracted further with ethyl acetate. The aqueous phase was concentrated *in vacuo*, the residue taken up in methanol and inorganics removed by filtration. Subsequent concentration gave the title compound (1.4g) as a beige solid; δH [$^2H_6$]DMSO 8.96 (1H,s), 8.50 (1H,s), 8.27 (1H,s); m/z ($M+1^+$) 216.

6-(5-Methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-one

6-(1,2,3,4-Tetrazol-5-yl)-pyrido[3,4-d]pyrimidin-4-one (1.4g) in acetic anhydride (10ml) was heated at reflux under N_2 for 2.5 hours. The cooled mixture was

absorbed onto silica and purified by chromatography to give the title compound (0.14g) as a beige solid; δH [$^2H_6$]DMSO 13.0(1H,bs), 9.30 (1H,s), 8.66 (1H,s), 8.47 (1H,s) 2.75 (3H,s); m/z ($M+1^+$) 230.

4-Chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidine

6-(5-Methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-one (0.5g) was treated with phosphorus oxychloride at room temperature under N_2. After 1 hour at room temperature and 1 hour at 50°C, the mixture was concentrated *in vacuo*, azeotroping with toluene, then taken up in ethyl acetate, washed with sodium bicarbonate solution, dried and concentrated *in vacuo* to give the title compound (0.17g) as an orange solid; δH $CDCl_3$ 9.68 (1H,s), 9.30 (1H,s), 8.96 (1H,s), 2.75 (3H,s); m/z ($M+1^+$) 248.

6-Benzyloxy-4-hydroxy-pyrido[3,4-d]pyrimidine

Sodium hydride (8.14g of 60% dispersion with mineral oil, 203.5mmol) was suspended in benzyl alcohol (200ml) under a nitrogen atmosphere. 6-Chloropyrido[3,4-d]pyrimidine (9.081g, 50.0mmol) was added and the mixture was heated at 150°C for 18 hours. When cool, the mixture was partitioned between water (200ml) and ether (200ml), the layers were separated, and the aqueous layer was washed with further ether. The aqueous solution was then acidified to pH1 by the addition of dilute HCl causing the precipitation of the title compound as a cream solid (7.885g, 31.1mmol, 62%); δH [$^2H_6$]DMSO 8.71(1H,s), 7.89(1H,s), 7.25-7.48 (6H,m), 5.40 (2H,s); m/z ($M+1^+$) 254.

6-Benzyloxy-4-chloro-pyrido[3,4-d]pyrimidine

6-Benzyloxy-4-hydroxy-pyrido[3,4-d]pyrimidine (1.033g, 4.1mmol) was suspended in thionyl chloride (10ml) under a nitogen atmosphere. DMF (3 drops) was added and the mixture was heated to reflux with stirring for 5.5 hours to give a dark solution, and then left to stand under nitrogen overnight. The mixture was concentrated *in vacuo*, azeotroping twice with toluene to remove all traces of thionyl cloride and acidic by-products. The material was further dried for two hours *in vacuo* to give the title compound as a brown solid, used without further purification; δH [$^2H_6$]DMSO 8.77(1H,s), 8.13(1H,s), 7.30-7.52 (6H,m), 5.45 (2H,s).

(3-Methyl-3-oxetane)methyl 2-furoate

2-Furoic acid (9.0g, 80.3mmol) was added to a solution of 3-methyl-3-oxetanemethanol (16.5g, 161.6mmol), 1,3-dicyclohexylcarbodiimide (25.0g, 121.1mmol) and DMAP (0.50g, 4.1mmol) in dichloromethane (250ml), and the mixture was stirred under a nitrogen atmosphere overnight. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give an oil. Crystallisation from ethanol/water gave a white solid collected by filtration, which was shown by NMR to be 2-furoic acid. The filtrate was concentrated *in vacuo* to remove the ethanol, and the resulting aqueous solution was extracted with dichloromethane (x2). The combined dichloromethane extracts were dried ($MgSO_4$) and concentrated to give the title compound as a colourless oil (11.8g, 60.1mmol, 75%); δH [$^2H_6$]DMSO 8.00 (1H,s), 7.34 (1H,d), 7.71 (1H, dd), 4.44 (2H,d), 4.35 (2H,s), 4.28 (2H,d), 1.31 (3H,s).

2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)furan

(3-Methyl-3-oxetane)methyl 2-furoate (11.8g, 60.1mmol) was dissolved in dichloromethane (250ml) and the solution was cooled to 0°C. Boron trifluoride-etherate (10 drops) was added and the mixture stirred at room temperature, and then left to stand for two months. Triethylamine (0.5ml, 0.36g, 3.6mmol) was added and the mixture concentrated to give a sticky white solid. Trituration with ether/acetone gave the title compound as a white solid (2.2g, 11.2mmol, 19%); δH [$^2H_6$]DMSO 8.00 (1H,s), 7.34 (1H,d), 7.71 (1H, dd), 4.44 (2H,d), 4.35 (2H,s), 4.28 (2H,d), 1.31 (3H,s).

5-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-2-[tri(*n*-butyl)stannyl]furan

2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)furan (2.0g, 10.2mmol) was dissolved in THF (20ml) and the solution was cooled to -78°C. *n*-BuLi (1.6M solution in hexanes, 7.7ml, 12.32mmol) was added and the mixture stirred at -78°C for 30min, allowed to warm to 0°C for 20 min. and then recooled to -78°C. The tributyltin chloride (3.5ml, 4.68g, 14.4mmol) was added and stirring was continued at -78°C for 15min. The mixture was allowed to warm gradually to room temperature and stirring continued for three days. The reaction was quenched by the addition of water, and extracted with ethyl acetate. This solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound as

a yellow oil (4.7g, 9.7mmol, 95%); δH [$^2H_6$]DMSO 6.52 (1H,d), 6.38 (1H, d), 3.96 (6H,s), 0.77-1.63 (30H,m).

(1-Benzyl-1H-indazol-5-yl)-(6-[5-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-furan-2-yl]-pyrido-[3,4-d]pyrimidin-4-yl)-amine

(1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido-[3,4-d]pyrimidin-4-yl)-amine (0.425g, 1.10mmol), 5-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-2-[tri(*n*-butyl)stannyl]furan (1.95g, 4.0mmol) and 1,4-bis(diphenylphosphino)butane palladium (II) chloride (0.068g, 0.11mmol) were reacted in dry dioxane (15ml) according to Procedure B. Purification by silica gel chromatography, eluting with 50-100% ethyl acetate/*i*-hexane, gave the title compound as a yellow solid (0.451g, 0.929mmol, 86%); δH [$^2H_6$]DMSO 10.58 (1H,s), 9.14 (1H,s), 8.71 (1H,s), 8.61 (1H,s), 8.16-8.21 (2H,m), 7.68-7.79 (2H,m), 7.22-7.36 (5H,m), 7.13 (1H,d), 6.68 (1H,d), 5.69 (2H,s), 4.06 (6H,s), 0.86 (3H,s); m/z ($M+1^+$) 547.

Examples

Example 1

(1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 1-benzyl-1H-indazol-5-ylamine and 4,6-dichloro-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]-DMSO 9.08 (1H,s), 8.92 (1H,s), 8.82 (1H,s), 8.23 (1H,d), 8.19 (1H,s), 7.80 (1H,d), 7.70 (1H,dd), 7.38-7.22 (5H,m), 5.69 (2H,s); m/z $(M + 1)^+$ 387.

Example 2

N4-(1-Benzyl-1H-indazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine

A stirred solution of (1-benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine (0.5g) in 33% aqueous dimethylamine (5ml) was heated at 130°C in a reacti-vial for 17 hr. The cooled mixture was dissolved in chloroform, absorbed onto silica and chromatographed to give the title compound (Procedure C) as a yellow solid; δH [$^2H_6$]-DMSO 9.00(1H,s), 8.51(1H,s), 8.09(2H,d), 7.55(1H,dd), 7.25(7H,m), 6.39(1H,m), 5.60(2H,s) 3.20 (6H,s); m/z $(M + 1)^+$ 396.

Alternatively, 4-chloro-6-(*N*,*N*-dimethylamino)-pyrido[3,4-d]pyrimidine and 5-amino-1-benzyl-1H-indazole were reacted according to Procedure A to give the title

compound as the hydrochloride salt; δH [$^2H_6$]DMSO 11.82(1H,s), 8.95(1H,s), 8.63(1H,s), 8.25(1H,s), 8.15(1H,s), 7.87(1H,d), 7.78(1H,s), 7.70(1H,dd), 7.30(5H,m), 5.79(2H,s), 3.23(6H,s); $C_{23}H_{22}N_7Cl$ requires C 63.96%, H 5.13%, N 22.70%; found C 63.44%, H 4.99%, N 22.74%.

The hydrochloride salt was partitioned between dichloromethane and 2N sodium carbonate. Extraction of the aqueous layer with dichloromethane was followed by drying of the organic phase and concentration *in vacuo* to give the free base.

Example 3

(1-Benzyl-1H-indazol-5-yl)-6-(N-(2-hydroxyethyl)-N-methylamino)-pyrido[3,4-d]pyrimidin-4-yl)-amine

A stirred solution of (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine (0.2g) in 2-methylaminoethanol (4ml) was heated at 130°C in a reacti-vial for 96 hr (Procedure C). The cooled mixture was partitioned between ethyl acetate and water. The aqueous phases were extracted with ethyl acetate. The dried extracts were concentrated *in vacuo* and the residue purified by flash chromatography to give the title compound as a yellow solid; δH [$^2H_6$]-DMSO/$CDCl_3$ 9.00(1H,s), 8.85(1H,s), 8.45(1H,s), 8.10(2H,d), 7.64(1H,dd), 7.30(7H,m), 7.08(1H,s),5.60(2H,s), 3.85(4H,m), 3.25 (3H,s); m/z $(M + 1)^+$ 426.

Example 4

(1-Benzyl-1H-indazol-5-yl)-(pyrido[3,4-d]pyrimidin-4-yl)-amine

A stirred solution of (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine (0.165g), 2-(tri-n-butylstannyl)furan (0.139g) and bis-(triphenylphosphine)palladium (II) chloride (30mg) in dioxane (10ml) was heated at reflux under nitrogen for 65 hr (Procedure B). The cooled mixture was absorbed onto silica and chromatographed to give the title compound as an orange solid; δH $CDCl_3$ 9.34(1H,s), 8.82(1H,s), 8.70(1H,d), 8.15(1H,d), 8.10(1H,s), 7.65(1H,d), 7.60(1H,s),7.53(1H,dd), 7.40(1H,d), 7.25(6H,m), 5.60(2H,s); m/z $(M + 1)^+$ 353.

Example 5

(2-Benzyl-1H-benzimidazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine

Prepared according to Procedure A from 5-amino-2-benzyl-1H-b nzimidazole and 4,6-dichloro-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]-DMSO 9.13(1H,s), 8.93(1H,s),

8.84(1H,s), 8.60(1H,s), 8.05(1H,dd), 7.88(2H,d), 7.50(6H, m), 4.61(2H,s); m/z (M + 1)$^+$ 387.

Example 6

N4-(1-Benzyl-1H-indol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine

The title compound was prepared from (1-benzyl-1H-indol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine by an analogous method to Example 2 (Procedure C) as a yellow solid; δH $CDCl_3$ 8.98(1H,s), 8.50(1H,s), 7.93(1H,s), 7.30(5H,m), 7.15(2H,m), 6.60(1H,d), 6.38(1H,s), 5.35(2H,s), 3.20(6H,s); m/z (M + 1)$^+$ 395.

Example 7

N4-(2-Benzyl-1H-benzimidazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]-pyrimidine-4,6-diamine

The title compound was prepared from (2-benzyl-1H-benzimidazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine by an analogous method to Example 2 (Procedure C) as a yellow solid; δH [$^2H_6$]-DMSO 9.75(1H,s), 8.80(1H,s), 8.32(1H,s), 8.08(1H,bs), 7.50(2H,m), 7.30(5H,m), 4.20(2H,s); m/z (M + 1)$^+$ 396.

Example 8

(1-Benzyl-1H-indazol-5-yl)-(6-(5-[1,3-dioxolan-2-yl]-furan-2-yl)-pyrido[3,4-d]-pyrimidin-4-yl)-amine

(1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine (4.28g), 2-(tributylstannyl)-5-(1,3-dioxolan-2-ylmethyl)-furan (J. Chem Soc., Chem. Commun., (1988), p560) (10g) and 1,4-bis(diphenylphosphino)butane palladium (II) chloride (1g) were heated at reflux in dioxane (150ml) for 24 hr (Procedure B). The solvent was removed *in vacuo* and the residue chromatographed on silica. Subsequent trituration gave the title compound as a yellow solid; δH [$^2H_6$] -DMSO 10.46 (1H, s), 9.17 (1H, s), 8.74 (1H, s), 8.52 (1H, s), 8.23 (1H, s), 8.18 (1H, s), 7.80-7.68 (2H, m), 7.41-7.22 (5H, m), 7.17 (1H, d), 6.80 (1H, d), 6.06 (1H, s), 5.71 (2H, s), 4.20-3.96 (4H, m).

Example 9

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde

(1-Benzyl-1H-indazol-5-yl)-(6-(5-[1,3-dioxolanyl]-furan-2-yl)-pyrido[3,4-d]-pyrimidin-4-yl)-amine (3.03g) and 2N HCl (50ml) were stirred in THF (50ml) for 16 hr. The resulting precipitate was filtered and washed with water to give thehydrochloride salt of the product; δH [$^2H_6$]DMSO 11.70 (1H,s), 9.74 (1H,s) 9.30 (1H,s), 9.27 (1H,s), 8.85 (1H,s), 8.23 (1H,s), 8.18 (1H,s), 7.68-7.87 (3H,m), 7.55 (1H,d), 7.22-7.38 (5H,m), 5.71 (2H,s). Subsequent neutralisation with triethylamine in ethanol/water gave the title compound; δH [$^2H_6$] -DMSO 9.64(1H,s), 9.19 (1H,s), 9.09(1H,s), 8.72(1H,s), 8.12(2H,m), 7.71(2H,m), 7.63(1H,dd), 7.43(1H,d), 7.20(5H,m), 5.62(2H,s).

Example 10

(2S)-1-(5-(4-(1-Benzyl-1H-indazol-5-ylamino)-6-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide hydrochloride

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde (800mg) and L-prolinamide (1.0g) were mixed in dichloromethane (8ml) at 25°C for 1 hr. The solution was cooled to 0°C and sodium triacetoxyborohydride (2.0g) was added. After 4 hr at 25°C the reaction mixture was subjected to flash chromatography directly on silica using 3% methanol in chloroform, to give the free base as a yellow solid; δH [$^2H_6$]DMSO 10.33 (1H,s), 9.13(1H,s) 8.65 (1H,s), 8.61 (1H,s), 8.26 (1H,s), 8.16 (1H,s), 7.75 (2H,m), 7.12-7.33 (7H,m), 7.09 (1H,d), 6.56 (1H,d), 5.69 (2H,s), 3.84 (2H,s), 3.31-3.39 (1H, obscured by water), 3.09-3.14 (2H,m), 1.70-2.20 (4H,m); m/z ($M+1^+$) 545. Treatment with saturated HCl in ethyl acetate gave the title compound; δH [$^2H_6$] -DMSO 12.25 (1H, s), 9.52(1H, s), 9.27 (1H, s), 8.80(1H, s), 8.53(1H, s), 8.27(1H, s), 8.21(1H, s), 7.83(2H, m), 7.72(1H, s), 7.30(6H, m), 6.93(1H, d), 5.72(2H, s), 4.88(1H, m), 4.60(2H, s), 3.20(2H, s), 1.90(4H, m); m/z $(M + 1)^+$ 545.

Example 11

(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-3H-imidazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine

(1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine (0.70g, 1.81mmol), 1-m thyl-5-[tri(*n*-butyl)stannyl]imidazole (prepared according to the

published method: K. Gaare et. al., Acta Chem. Scand., (1993), 47(1), p57-62) (2.2g, 6mmol), 1,4-bis(diphenylphosphino)-butane palladium (II) chloride (0.41g, 0.7mmol) and silver oxide (0.224g, 1.8mmol) were reacted in dry dioxane according to Procedure B. Purification by silica gel chromatography, eluting with 10%MeOH/EtOAc, gave the product as a pale brown solid (0.16g, 0.37mmol, 20%); δH $CDCl_3$ 10.62 (1H,s), 9.25 (1H,s), 8.75 (1H,s), 8.60 (1H,s), 8.13 (1H,s), 8.03 (1H,s), 7.20-7.78 (9H,m), 5.61 (2H,s), 3.96 (3H,s); m/z ($M+1^+$) 433.

Example 12

N6,N6-Dimethyl-N4-(1-pyridin-2-ylmethyl-1H-indazol-5-yl)-pyrido[3,4-d]pyrimidine-4,6-diamine hydrochloride

Prepared according to Procedure A from 1-(2-Pyridylmethyl)indazol-5-ylamine and 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.75(1H,s), 9.92(1H,s), 8.62(1H,s), 8.55(1H,d), 8.24(1H,s), 8.14(1H,s), 7.75(4H,m), 7.33(1H,m), 7.08(1H,d), 5.82(2H,s), 3.20(6H,s); m/z ($M+1^+$) 397.

Example 13

N6,N6-Dimethyl-N4-(1-pyridin-3-ylmethyl-1H-indazol-5-yl)-pyrido[3,4-d]pyrimidine-4,6-diamine hydrochloride

Prepared according to Procedure A from 1-(3-Pyridylmethyl)-1H-indazol-5-ylamine and 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.50(1H,s), 9.90(1H,s), 8.65(1H,d), 8.60(2H,m), 8.25(1H,s), 8.14(1H,s), 7.91(1H,d), 7.75(2H,m), 7.70(1H,s), 7.50(1H,m), 5.80(2H,s), 3.20(6H,s); m/z ($M+1^+$) 397.

Example 14

N4-(1-Benzyl-3-methyl-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine

Prepared according to Procedure A from 1-Benzyl-3-methyl-1H-indazol-5-ylamine and 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.75(1H,s), 8.90(1H,s), 8.62(1H,s), 8.02(1H,s), 7.70(3H,m), 7.30(5H,m), 5.62(2H,s), 3.30(6H,s) 2.50(3H,s); m/z ($M+1^+$) 410.

Example 15

N4-(1-(2-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine hydrochloride

Prepared according to Procedure A from 1-(2-Fluoro-benzyl)-1H-indazol-5-ylamine and 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.45(1H,s), 8.90(1H,s), 8.63(1H,s), 8.24(1H,s), 8.13(1H,s), 7.87(1H,d), 7.70(1H,d), 7.62(1H,s), 7.36(1H,m), 7.20 (3H,m), 5.75(2H,s), 3.22(6H,s); m/z (M^+) 413.

Example 16

N4-(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine hydrochloride

Prepared according to Procedure A from 1-(3-Fluoro-benzyl)-1H-indazol-5-ylamine and 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.52(1H,s), 8.90(1H,s), 8.60(1H,s), 8.24(1H,s), 8.14(1H,s), 7.85(2H,m), 7.70(1H,d), 7.49(1H,m), 7.10 (3H,m), 5.72(2H,s), 3.19(6H,s); m/z ($M+1^+$) 414.

Example 17

N4-(1-(4-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine hydrochloride

Prepared according to Procedure A from 1-(4-Fluoro-benzyl)-1H-indazol-5-ylamine and 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.42(1H,s), 8.90(1H,s), 8.60(1H,s), 8.22(1H,s), 8.14(1H,s), 7.86(1H,d), 7.65(1H,d), 7.61(1H,s), 7.32(2H,dd), 7.17 (2H,dd), 5.70(2H,s), 3.23(6H,s); m/z (M^+) 414.

Example 18

N4-(1-Benzenesulphonyl-1H-indol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine hydrochloride

Prepared according to Procedure A from 1-benzenesulphonyl-1H-indol-5-ylamine and 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.64(1H,s), 8.90(1H,s), 8.60(1H,s), 8.05(4H,m), 7.90(1H,d), 7.65(5H,m), 6.92(1H,d), 3.20(6H,s); m/z (M^+) 445.

Example 19

N4-(3-Benzenesulphonyl-1H-indol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine hydrochloride

Prepared according to Procedure A from 3-benzenesulphonyl-1H-indol-6-ylamine and 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.55(1H,s), 11.50(1H,s), 8.90(1H,s), 8.60(1H,s), 8.79(1H,d), 8.00(3H,m), 7.86(1H,d), 7.60(5H,m), 3.20(6H,s); m/z (M^+) 445.

Example 20

(1-Benzyl-1H-indazol-5-yl)-(6-imidazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine

Imidazole (0.8g) in dry DMSO was treated with sodium hydride (60%, 0.47g) and (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine in a reacti-vial and heated at 120°C. After 7 days, the mixture was poured onto water and extracted with ethyl acetate. Purification using a Bond Elute ™ cartridge gave the title compound as a brown solid after trituration from water; δH [$^2H_6$]DMSO 10.28(1H,s), 9.25(1H,s), 8.90(1H,s), 8.78(1H,s), 8.67(1H,s), 8.40(1H,s), 8.30(1H,s), 8.10(1H,s), 7.88(2H,m), 7.40(5H,m), 5.70(2H,s); m/z (M^+) 419.

Example 21

(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,4-triazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine

1,2,4-triazole was reacted with (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine as in Example 20 to give the title compound; δH [$^2H_6$]DMSO 10.53(1H,s), 9.46(1H,s), 9.14(1H,s), 9.01(1H,s), 8.65(1H,s), 8.40(1H,s), 8.25(1H,s), 8.15(1H,s), 7.75(2H,s), 7.25(5H,m), 5.65(2H,s); m/z (M^+) 418.

Example 22

(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,3-triazol-2-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine

1,2,3-triazole was reacted with (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine as in Example 21 to give the title compound; δH [$^2H_6$]DMSO 10.62(1H,s), 9.24(2H,s), 8.73(1H,s), 8.33(3H,s), 8.21(1H,s), 7.80(1H,s), 7.33(5H,m), 5.73(2H,s); m/z (M^+) 420.

Example 23

(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,3-triazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine

1,2,3-triazole was reacted with (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine as in Example 21 to give the title compound; δH [$^2H_6$]DMSO 10.53(1H,s), 9.28(1H,s), 9.13(1H,s), 8.89(1H,s), 8.64(1H,s), 8.23(1H,s), 8.10(1H,s), 8.00(1H,s), 7.69(2H,s), 7.23(5H,m), 5.62(2H,s); m/z (M^+) 420.

Example 24

(1-Benzyl-1H-indazol-5-yl)-(6-pyrrolidin-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine

Pyrrolidine (2ml) was reacted with (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine (0.4g) in a reacti-vial at 100°C (Procedure C). After 18 hours, the cooled mixture was poured onto water and the precipitate washed with hot ether and crystallised from acetone to give the title compound; δH [$^2H_6$]DMSO 10.53(1H,s), 9.75(1H,s), 8.79(1H,s), 8.30(1H,s), 8.23(1H,s), 8.14(1H,s), 7.70(2H,m), 7.28(5H,m), 7.14(1H,s), 5.68(2H,s) 3.50(4H,m), 2.02(4H,m); m/z (M^+) 422.

Example 25

(1-Benzyl-1H-indazol-5-yl)-(6-piperidin-1-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine

Piperidine was reacted with(1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine as in Example 24 to give the title compound (Procedure C); δH [$^2H_6$]DMSO 9.80(1H,s), 8.80(1H,s), 8.33(1H,s), 8.22(1H,s), 8.15(1H,s), 7.70(2H,m), 7.50(1H,s), 7.28(5H,m), 5.68(2H,s) 3.65(4H,m), 1.65(6H,m); m/z (M^+) 436.

Example 26

N4-(1-Benzyl-1H-indazol-5-yl)-N6-ethyl-N6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine

Ethylmethylamine was reacted with (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine as in Example 2 to give the title compound (Procedure C); δH [$^2H_6$]DMSO 9.87(1H,s), 8.86(1H,s), 8.37(1H,s), 8.25(1H,s), 8.20(1H,s), 7.76(2H,m), 7.35(5H,m), 5.75(2H,s) 3.79(2H,q), 3.18(3H,s), 1.19(3H,t); m/z (M^+) 410.

Example 27

2-(4-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-piperazin-1-yl)-N-isopropyl-acetamide

4-Isopropylacetamido-1,4-piperazine (Aldrich) was reacted with (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine as in Example 24 to give the title compound (Procedure C); δH [$^2H_6$]DMSO 8.85(1H,s), 8.35(1H,s), 8.20(2H,d), 7.72(2H,m), 7.55(1H,s), 7.30(5H,m), 5.70(2H,s) 3.95(1H,m), 3.68(4H,bs), 3.00(2H,s), 2.60(4H,bs), 1.10(6H,d); m/z (M^+) 535.

Example 28

2-(4-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-piperazin-1-yl)-1-morpholin-4-yl-ethanone

N-Morpholinylacetamido-1,4-piperazine (Emkachem) was reacted with (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine as in Example 24 to give the title compound (Procedure C); δH [$^2H_6$]DMSO 9.80(1H,s), 8.83(1H,s), 8.38(1H,s), 8.22(1H,s), 8.15(1H,s), 7.75(1H,d), 7.66(1H,dd), 7.55(1H,s), 7.28(5H,m), 5.70(2H,s) 3.60(10H,m), 3.50(2H,m), 3.28(3H,s), 2.62(4H,bs); m/z (M^+) 564.

Example 29

(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine hydrochloride

4-Chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl) pyrido[3,4-d]pyrimidine (0.02g) was reacted with 1-benzylindazol-5-ylamine according to Procedure A to give the title compound as a yellow solid; δH [$^2H_6$]DMSO 11.50(1H,s), 9.55(1H,s), 9.43 (1H,s), 8.95(1H,s), 8.34(2H,m), 7.91(1H,d), 7.83(1H,dd), 7.40(5H,m), 5.80 (2H,s), 2.75 (3H,s); m/z ($M+1^+$) 435.

Example 30

(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 1-(3-Fluoro-benzyl)-1H-indazol-5-ylamine and 4-chloro-6-(5-methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.50(1H,s), 9.53(1H,s), 9.41(1H,s), 8.94(1H,s), 8.30(2H,s), 7.90(1H,d), 7.80(1H,dd), 7.45(1H,d), 7.25(3H,m), 5.80(2H,s), 2.75 (3H,s); m/z ($M+1^+$) 453.

Example 31

(1-Benzyl-1H-indol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine hydrochloride

Prepared according to Procedure A from 1-benzyl-1H-indol-5-ylamine and 4,6-dichloro-pyrido[3,4-d]pyrimidine; δH [$^2H_6$]DMSO 11.45(1H,s), 9.08(1H,s), 8.95(1H,s), 8.80(1H,s), 7.98(1H,d), 7.60(2H,m), 7.30(6H,m), 6.60(1H,d), 5.48(2H,s); m/z ($M+1^+$) 386.

Example 32

(1-Benzyl-1H-indazol-5-yl)-(6-(4-methyl-piperazin-1-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine

4-Methylpiperazine was reacted with (1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine as in Example 24 to give the title compound (Procedure C); δH [$^2H_6$]DMSO 9.80(1H,s), 8.82(1H,s), 8.47(1H,s), 8.23(1H,s), 8.15(1H,s), 7.75(1H,d), 7.67(1H,d), 7.54 (1H,s), 7.28(5H,m), 5.68(2H,s) 3.64(4H,m), 3.34(4H,m), 2.27(3H,s); m/z (M^+) 451.

Example 33

(1-Benzyl-1H-indazolyl-5-yl)-(6-benzyloxy-pyrido[3,4-d]pyrimidin-4-yl)-amine hydrochloride

6-Benzyloxy-4-chloro-pyrido[3,4-d]pyrimidine (0.54g, *ca.*2mmol) and 5-amino-1-benzyl-1H-indazole (0.458g, 2.05mmol) were reacted according to Procedure A to give the title compound as a yellow solid (0.740g, 1.50mmol, 75%); δH [$^2H_6$]DMSO 11.50 (1H,s), 9.00 (1H,s), 8.77 (1H,s), 8.16-8.33 (3H,m), 7.83 (1H,d), 7.71 (1H,dd), 7.13-7.58 (10H,m), 5.69 (2H,s), 5.55 (2H,s); m/z ($M+1^+$) 459.

Example 34

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesuphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido-[3,4-d]pyrimidin-4-yl)-amine hydrochloride

5-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde (0.70g, 1.81mmol), 2-(methanesulphonyl)ethylamine hydrochloride (1.30g, 8.14mmol) and triethylamine (0.65ml, 0.47g, 4.7mmol) were stirred in dichloromethane (7ml) at room temperature for 1 hour forming a precipitate. The mixture was cooled to 0°C and sodium triacetoxyborohydride (1.60g, 7.5mmol) was added. The temperature was maintained at 0°C for 15min and then stirring was continued at room temperature overnight. The reaction mixture was diluted with

water, and the resulting pale yellow precipitate was collected and washed with water and acetone. This was resuspended in a mixture of acetone and methanol and acidified with ethereal HCl. The solvents were removed *in vacuo* and the residue suspended in acetone and collected by filtration. This was dried at 60°C *in vacuo* to give the product as an orange-yellow solid (0.40g, 0.64mmol, 35%); δH [$^2H_6$]DMSO 11.40 (1H,s), 9.88 (1H,br s), 9.52 (1H,s), 9.22 (1H,s), 8.80 (1H,s), 8.31 (1H,s), 8.19 (1H,s), 7.77-7.90 (2H,m), 7.21-7.37 (6H,m), 6.98 (1H,d), 5.70 (2H,s),4.47 (2H,d), 3.42-3.80 (4H,m, obscured by water), 3.14 (3H,s); m/z ($M+1^+$) 554.

Example 35

5-[4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido-[3,4-d]pyrimidin-6-yl]-furan-2-carboxylic acid hydrochloride

(1-Benzylindazol-5-yl)-(6-[5-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-furan-2-yl]-pyrido-[3,4-d]pyrimidin-4-yl)-amine (0.445g, 0.81mmol) was suspended in a mixture of THF (15ml) and dilute HCl (15ml) and stirred at room temperature for 18 hours. The mixture was diluted with water to preciptate the intermediate (partial hydrolysis) which was collected by filtration and washed with water. This solid was suspended in a mixture of THF (10ml) and NaOH (1M, 10ml) and stirred at room tmperature for 18 hours. The THF was removed *in vacuo* and the residue was acidified to pH1 with dilute HCl to give the product as an orange solid, which was collected by filtration (0.322g, 0.645mmol, 79%); δH [$^2H_6$]DMSO 10.63 (1H,s), 9.19 (1H,s), 8.89 (1H,s), 8.64 (1H,s), 8.17-8.22 (2H,m), 7.67-7.80 (2H,m), 7.46 (1H,s), 7.23-7.39 (6H,m), 5.70 (2H,s); m/z ($M+1^+$) 463.

Example 36

5-[4-(1-benzyl-1H-indazol-5-ylamino)-pyrido-[3,4-d]pyrimidin-6-yl]-furan-2-carboxylic acid 2-methanesulphonyl-ethylamide hydrochloride

5-[4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido-[3,4-d]pyrimidin-6-yl]-furan-2-carboxylic acid hydrochloride (0.125g, 0.25mmol) and carbonyl diimidazole (0.052g, 0.33mmol) were suspended in dry THF (3ml) under a nitrogen atmosphere and stirred at room temperature for 7 hours. 2-(Methanesulphonyl)ethylamine hydrochloride (0.080g, 0.50mmol) and triethylamine (0.15ml, 0.11g, 1.08mmol) were added, together with further THF (2ml), and the resulting mixture was stirred at room temperature for 18 hours. The mixture was adsorbed onto silica gel and purified by column

chromatography, eluting with 2-10% MeOH/DCM. Concentration of the relevant fractions gave a pale yellow solid. This was resuspended in methanol and treated with ethanolic HCl to give the product as an orange solid, which was collected by filtration, washed with methanol, acetone and ether, and dried *in vacuo* (0.093g, 0.154mmol, 61%); δH [$^2H_6$]DMSO 12.00 (1H,s), 9.76 (1H,s), 9.19-9.29 (2H,m), 8.75 (1H,s), 8.28 (1H,s), 8.22 (1H,s), 7.78-7.90 (2H,m), 7.23-7.38 (7H,m), 5.71 (2H,s), 3.50-3.90 (2H obscured by water signal), 3.48 (2H,t), 3.07 (3H,s); m/z ($M+1^+$) 568.

Examples 37 and 38

*N*4-(1-Benzyl-1H-indazol-5-yl)-*N*6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine; N4-[1-(4-Hydroxybenzyl)-1H-indazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine

Prepared by incubation of N4-(1-Benzyl-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine with *Streptomyces rimosus subsp. paromomycinus* (NRRL 2455). The micro-organism was stored frozen (-80°C) on porous beads in cryovials containing cryopreservative (Microbank™ beads, Richmond Hill, Ontario, Canada). A single bead was used to inoculate each of 2 x 50ml aliquots of culture medium (SB1) dispensed in 250ml Erlenmeyer flasks.

The microorganism was grown in SB1 medium at a temperature of 28°C. Flasks were shaken at 250rpm. The SB1 culture medium consisted of Arkasoy (25g; British Arcady Company), Bacto yeast extract (5g; Difco Laboratories) and KH_2PO_4 (5g) in distilled water (900ml). The pH of the culture medium was adjusted to 7.2 using conc. NaOH prior to autoclaving (15min./121°C). 100ml of a 20% (w/v) solution of glucose (filter sterilised) was added post sterilisation.

N4-(1-Benzyl-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine (12.5mg) in methanol (1.0ml) was added to each culture flask after 72 hours growth. Cultures were harvested 7 days after compound addition.

Isolation: The culture broth (2 x 50ml) was mixed with an equal volume of methanol (containing 0.6% (v/v) TFA), centrifuged (4000rpm, 4.C, 30min) and the supernatant concentrated under a stream of nitrogen gas. The resulting concentrated aqueous extract was adsorbed onto a water-equilibrated C18 SPE cartridge (2g; Varian Ltd., Walton-on Thames, UK) which was washed with water (5 volum s), then eluted with

3 x 5ml methanol (containing 0.3% (v/v) TFA). The eluent was then diluted (mobile phase A, 10ml) and filtered (0.2mm PTFE filter) prior to preparative HPLC using the following system: - Spherisorb SB5 C6 15cm x 20mm, flow rate 20ml/min, detection wavelength 232nm; mobile phase A: 50mM ammonium acetate containing 3ml/l TFA; mobile phase B: 50% acetonitrile, 50mM ammonium acetate containing 3ml/l TFA; gradient: 0 to 30 min, 100%A - 100%B; 30 to 35 min, 100%B; 35 to 37 min, 100%B - 100%A; 37 to 40 min, 100%A. Appropriate fractions were adsorbed onto water-equilibrated C18 SPE cartridges (200mg; Varian Ltd., Walton-on-Thames, UK), which were washed with water (5 volumes) then eluted with 2 x 1ml methanol (containing 0.3% (v/v) TFA). The solvent was removed *in vacuo* to yield the title compounds.

From the incubation was obtained:

*N*4-(1-Benzyl-1H-indazol-5-yl)-*N*6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine (0.9mg); δH [$^2H_6$]DMSO 10.95 (1H,s), 8.79 (1H,s), 8.63 (1H,s), 8.21 (1H,s), 8.15 (1H,s),7.82 (1H,d), 7.67 (1H,d), 7.20-7.38 (6H,m), 5.71 (2H,s), 2.91 (3H,s); and N4-[1-(4-Hydroxybenzyl)-1H-indazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine (1.5mg); δH [$^2H_6$]DMSO 11.30 (1H,s), 9.55 (1H,br s), 8.89 (1H,s), 8.73 (1H,s), 8.20 (1H,s), 8.09 (1H,s),7.84 (1H,d), 7.64 (1H,d), 7.50 (1H,s), 7.17 (2H,d), 6.71 (2H,d), 5.58 (2H,s), 3.20 (6H,s).

Examples 39 to 41

The following compounds (and their hydrochlorides, if appropriate) are prepared by analogous techniques using the appropriate starting materials:

N4-[1-(*S*,*R*-α-Methylbenzyl)-1H-indazol-5-yl]-*N*6,*N*6-dimethyl-pyrido-[3,4-d]pyrimidin-4,6-diamine;

N4-(3-Benzylsulphonyl-1H-indazol-6-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]-pyrimidine-4,6-diamine;

N4-(3-Benzyl-1H-indazol-6-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]-pyrimidine-4,6-diamine.

Biological Data

Compounds of the present invention were tested for protein tyrosine kinase inhibitory activity in substrate phosphorylation assays and cell proliferation assays.

The substrate phosphorylation assays use baculovirus expressed, recombinant constructs of the intracellular domains of c-erbB-2 and c-erbB-4 that are constitutively active and EGFr isolated from solubilised A431 cell membranes. The method measures the ability of the isolated enzymes to catalyse the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide (Biotin-GluGluGluGluTyrPheGluLeuVal). The enzyme is incubated for 30 minutes, at room temperature, with 10mM $MnCl_2$, ATP and peptide at Km concentrations, and test compound (diluted from a 5mM stock in DMSO, final DMSO concentration is 2%) in 40mM HEPES buffer, pH 7.4. The reaction is stopped by the addition of EDTA (final concentration 0.15mM) and a sample is transferred to a streptavidin-coated 96-well plate. The plate is washed and level of phosphotyrosine on the peptide is determined using a Europium-labelled antiphosphotyrosine antibody and quantified with a time-resolved fluorescence technique. The results are shown in Table 1 as the IC_{50} values in nM.

The cell proliferation assay uses an immortalised human breast epithelial cell line (HB4a) which has been transformed by over-expression of c-erbB-2. Growth of these cells in low serum is dependent upon the c-erbB-2 tyrosine kinase activity. The specificity of the effect of the test compounds on tyrosine kinase dependent growth over general toxicity is assessed by comparison to an HB4a cell line which has been transfected with ras. Cells are plated at 3000/well in 96-well plates in 0.1 ml medium and allowed to attach overnight. test compound is added in 0.1 ml medium, with a final concentration of 0.5% DMSO, and the plates incubated for 4 days at 37°C. The cells are then examined microscopically for evidence of morphological detransformation and cell mass is estimated by staining with methylene blue and measuring the absorbance at 620nm. The results are shown in Table 1 below as the IC_{50} values in nM. Activity against a range of naturally occurring EGFr or c-erbB-2 over-expressing human tumour cell lines (BT474-breast, HN5-head and neck, N87-gastric and Calu3-lung) is assessed with selected compounds by the same methodology. The results are also shown in Table 1 below as the IC_{50} values in nM.

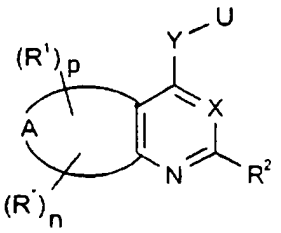
Table 1

Example	Substrate Phosphorylation			Cell Proliferation					
	EGFr	erbB-2	erbB-4	HB4a erbB-2	HB4a ras	BT474	N87	Calu3	HN5
1		27	48						
2	1	19	20	110	17000	140	240	380	300
3		7	23	140	33000			1800	
4		120	1300	3900	13000				
6		11	150						320
7		7	21	1900	19000	610		8000	
10		6	10	71	21000	2	2	160	130
11	15	9	55	1400	3800	1400	370	1200	1400
12	77	1	3	170	32000				
13	370	50	2400	240	28000				
14	830	430	1500	950	7900				
15		7	4	4	14000				
16		9	96	44	11000	1	120	180	81
17		250		490	7600	550		7000	
18	290	98	1700	21	19000				440
19	540	6	130	1200	33000				
20	4	33		470	14000				
21	54			500	18000				
22	22			1700	18000				
23	31			250	22000				
24		20	140	810	50000	460			900
25	380	60	570	480	>50000	270	940		

Example	Substrate Phosphorylation			Cell Proliferation					
	EGFr	erbB-2	erbB-4	HB4a erbB-2	HB4a ras	BT474	N87	Calu3	HN5
26	54	29		150	8900				
27		2	190	380	21000				
28		4	170	590	28000				
29	2	2	5500	5200	29000	11000	10000		
30	2	2	9600	2900	26000				
32		55	140	100	8800	1000	600	8200	4200
33	1900	140	2700	>50000	50000				
34		15	230	70	17000	2	190	1300	190
35	1600			27000	>50000				
36	1600			3100	>50000				
37	30	65	180	520	17000	1100	2200	3700	2000
38	930	330	1900	6900	50000				

Claims

1. A compound of formula (I):



(I)

or a salt or solvate thereof;

wherein X is N or CH;

Y is a group $W(CH_2)$, $(CH_2)W$, or W, in which W is O, $S(O)_m$ wherein m is 0, 1 or 2, or NR^a wherein R^a is hydrogen or a C_{1-8} alkyl group;

R" represents a phenyl group or a 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms selected from N, O or $S(O)_m$, wherein m is as defined above, with the proviso that the ring does not contain two adjacent O or $S(O)_m$ atoms, the phenyl group or the heterocyclic ring being optionally substituted by one or more R^1 groups; and n = 0 or 1;

each R^1 is independently selected from the group comprising amino, hydrogen, halogen, hydroxy, nitro, carboxy, formyl, cyano, trifluoromethyl, trifluoromethoxy, carbamoyl, ureido, guanidino, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkoxy, C_{4-8} alkylcycloalkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, N-C_{1-4} alkylcarbamoyl, N,N-di-[C_{1-4} alkyl]carbamoyl, hydroxyamino, C_{1-4} alkoxyamino, C_{2-4} alkanoyloxyamino, C_{1-4} alkylamino, di[C_{1-4} alkyl]amino, di-[C_{1-4} alkyl]amino-C_{1-4} alkylene-(C_{1-4} alkyl)amino, C_{1-4} alkylamino- C_{1-4} alkylene-(C_{1-4} alkyl)amino, hydroxy-C_{1-4} alkylene-(C_{1-4} alkyl)amino, phenyl, phenoxy, 4-pyridon-1-yl, pyrrolidin-1-yl, imidazol-1-yl, piperidino, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, piperazin-1-yl, 4-C_{1-4} alkylpiperazin-1-yl, dioxolanyl, C_{1-8} alkylthio, arylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, arylsulphinyl, arylsulphonyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl, C_{2-4} alkanoyloxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, carboxy-C_{1-4} alkyl, formyl-C_{1-4}

alkyl, C_{1-4} alkoxycarbonyl-C_{1-4}-alkyl, carbamoyl-C_{1-4} alkyl, N-C_{1-4} alkylcarbamoyl-C_{1-4}alkyl, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4}alkyl, amino-C_{1-4} alkyl, C_{1-4} alkylamino-C_{1-4} alkyl, di-[C_{1-4} alkyl]amino-C_{1-4} alkyl, phenyl-C_{1-4} alkyl, 4-pyridon-1-yl-C_{1-4} alkyl, pyrrolidin-1-yl-C_{1-4} alkyl, imidazol-1-yl-C_{1-4} alkyl, piperidino-C_{1-4} alkyl, morpholino-C_{1-4} alkyl, thiomorpholino-C_{1-4}alkyl, thiomorpholino-1-oxide-C_{1-4}alkyl, thiomorpholino-1,1-dioxide-C_{1-4}alkyl, piperazin-1-yl-C_{1-4}alkyl, 4-C_{1-4} alkylpiperazin-1-yl-C_{1-4} alkyl, hydroxy-C_{2-4} alkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkoxy-C_{1-4} alkyl, hydroxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylamino-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, hydroxy-C_{2-4} alkylthio-C_{1-4} alkyl, C_{1-4} alkoxy-C_{2-4} alkylthio-C_{1-4} alkyl, phenoxy-C_{1-4} alkyl, anilino-C_{1-4} alkyl, phenylthio-C_{1-4} alkyl, cyano-C_{1-4} alkyl, halogeno-C_{2-4} alkoxy, hydroxy-C_{2-4} alkoxy, C_{2-4} alkanoyloxy-C_{2-4} alkoxy, C_{1-4} alkoxy-C_{2-4} alkoxy, carboxy-C_{1-4} alkoxy, formyl-C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl-C_{1-4} alkoxy, carbamoyl-C_{1-4} alkoxy, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkoxy, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkoxy, amino-C_{2-4} alkoxy, C_{1-4} alkylamino-C_{2-4} alkoxy, di-[C_{1-4} alkyl]amino-C_{2-4} alkoxy, di-[C_{1-4} alkyl-C_{2-4} alkoxy]amino-C_{2-4} alkoxy, C_{2-4} alkanoyloxy, hydroxy-C_{2-4} alkanoyloxy, C_{1-4}alkoxy-C_{2-4} alkanoyloxy, phenyl-C_{1-4} alkoxy, phenoxy-C_{2-4} alkoxy, anilino-C_{2-4} alkoxy, phenylthio-C_{2-4} alkoxy, 4-pyridon-1-yl-C_{2-4} alkoxy, piperidino-C_{2-4} alkoxy, pyrrolidin-1-yl-C_{2-4} alkoxy, imidazol-1-yl-C_{2-4} alkoxy, morpholino-C_{2-4} alkoxy, thiomorpholino-C_{2-4} alkoxy, thiomorpholino-1-oxide-C_{2-4} alkoxy, thiomorpholino-1,1-dioxide-C_{2-4} alkoxy, piperazin-1-yl-C_{2-4} alkoxy, 4-C_{1-4} alkylpiperazin-1-yl-C_{2-4} alkoxy, halogeno-C_{2-4} alkylamino, hydroxy-C_{2-4} alkylamino, C_{2-4} alkanoyloxy-C_{2-4} alkylamino, C_{1-4} alkoxy-C_{2-4} alkylamino, carboxy-C_{1-4} alkylamino, C_{1-4} alkoxycarbonyl-C_{1-4} alkylamino, carbamoyl-C_{1-4} alkylamino, N-C_{1-4} alkylcarbamoyl-C_{1-4} alkylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{1-4} alkylamino, amino-C_{2-4} alkylamino, C_{1-4} alkylamino-C_{2-4} alkylamino, di-[C_{1-4}alkyl]amino-C_{2-4} alkylamino, phenyl-C_{1-4} alkylamino, phenoxy-C_{2-4} alkylamino, anilino-C_{2-4} alkylamino, 4-pyridon-1-yl-C_{2-4} alkylamino, pyrrolidin-1-yl-C_{2-4} alkylamino, imidazol-1-yl-C_{2-4} alkylamino, piperidino-C_{2-4} alkylamino, morpholino-C_{2-4} alkylamino, thiomorpholino-C_{2-4} alkylamino, thiomorpholino-1-oxide-C_{2-4} alkylamino, thiomorpholino-1,1-dioxide-C_{2-4} alkylamino, piperazin-1-yl-C_{2-4} alkylamino, 4-(C_{1-4} alkyl)piperazin-1-yl-C_{2-4} alkylamino , phenylthio-C_{2-4} alkylamino, C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonylamino, C_{1-4} alkylsulphonylamino, C_{1-4} alkylsulphinylamino, benzamido, benzenesulphonamido, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halogeno-C_{2-4}

alkanoylamino, hydroxy-C_{2-4} alkanoylamino, hydroxy-C_{2-4} alkanoyl-(C_{1-4} alkyl)-amino, C_{1-4} alkoxy-C_{2-4} alkanoylamino, carboxy-C_{2-4} alkanoylamino, C_{1-4} alkoxycarbonyl-C_{2-4} alkanoylamino, carbamoyl-C_{2-4} alkanoylamino, N-C_{1-4} alkylcarbamoyl-C_{2-4} alkanoylamino, N,N-di-[C_{1-4} alkyl]carbamoyl-C_{2-4} alkanoylamino, amino-C_{2-4} alkanoylamino, C_{1-4} alkylamino-C_{2-4} alkanoylamino or di-[C_{1-4} alkyl]amino-C_{2-4} alkanoylamino, and wherein said benzamido or benzenesulphonamido substituent or any anilino, phenoxy or phenyl group on a R^1 substituent may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents; and wherein any substituent containing a heterocyclic ring may optionally bear one or two halogeno, C_{1-4} alkyl or C_{1-4} alkoxy substituents on said ring; and wherein any substituent containing a heterocyclic ring may optionally bear one or two oxo or thioxo substituents on said ring;

or R^1 represents a group selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 wherein

M^1 represents a C_{1-4} alkyl group, wherein optionally a CH_2 group is replaced by a CO group;

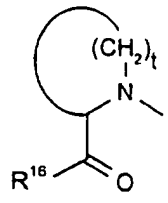
M^2 represents NR^{12} or $CR^{12}R^{13}$, in which R^{12} and R^{13} each independently represent H or C_{1-4} alkyl;

M^3 represents a C_{1-4} alkyl group;

$M^{3'}$ represents a C_{1-4} alkyl group or is absent;

M^4 represents CN, $NR^{12}S(O)_mR^{13}$, $S(O)_mNR^{14}R^{15}$, $CONR^{14}R^{15}$, $S(O)_mR^{13}$ or CO_2R^{13}, in which R^{12}, R^{13} and m are as hereinbefore defined and R^{14} and R^{15} each independently represent H or C_{1-4} alkyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring optionally containing 1 or 2 additional heteroatoms selected from N, O or $S(O)_m$ in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group, and which ring may optionally bear one or two oxo or thioxo substituents;

M^5 represents the group $NR^{14}R^{15}$, wherein R^{14} and R^{15} are as defined above, or M^5 represents the group



in which t represents 2 to 4 and R^{16} represents OH, OC_{1-4} alkyl or $NR^{14}R^{15}$; and

M^6 represents a C_{3-6} cycloalkyl group, the group $NR^{14}R^{15}$, wherein R^{14} and R^{15} are as defined above, or a 5- or 6-membered heterocyclic ring system containing 1 to 4 heteroatoms selected from N, O or S;

and p is 0 to 3; or when p is 2 or 3, two adjacent R^1 groups together form an optionally substituted methylenedioxy or ethylenedioxy group;

R^2 is selected from the group comprising hydrogen, halogen, trifluoromethyl, C_{1-4} alkyl and C_{1-4} alkoxy;

U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and $S(O)_m$, wherein m is 0,1 or 2 and wherein the ring system is substituted by at least one independently selected R^6 group and is optionally substituted by at least one independently selected R^4 group, with the proviso that U does not represent phenyl;

each R^4 is independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, di-[C_{1-4} alkyl]amino, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, di-[C_{1-4} alkyl] carbamoyl, carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro or trifluoromethyl;

each R^6 is independently a group ZR^7 wherein Z is joined to R^7 through a $(CH_2)p$ group in which p is 0, 1 or 2 and Z represents a group $V(CH_2)$, $V(CF_2)$, $(CH_2)V$, $(CF_2)V$, V(CRR'), V(CHR) or V where R and R' are each C_{1-4} alkyl and in which V is a hydrocarbyl group containing 0,1 or 2 carbon atoms, carbonyl, dicarbonyl, CH(OH), CH(CN), sulphonamide, amide, O, $S(O)_m$ or NR^b where R^b is hydrogen or R^b is C_{1-4} alkyl; and R^7 is an optionally substituted C_{3-6} cycloalkyl; or an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety;

or R^6 is a group ZR^7 in which Z is NR^b, and NR^b and R^7 together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety;

A represents a fused 5, 6 or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N, O or $S(O)_m$, wherein m is as defined above, the heterocyclic ring containing a total of 1, 2 or 3 double bonds inclusive of the bond in the pyridine or pyrimidine ring to which it is fused, with the provisos that the heterocyclic ring does not form part of a purine and that the fused heterocyclic ring does not contain two adjacent O or $S(O)_m$ atoms.

2. A compound as claimed in claim 1 wherein R^1 is as defined in claim 1 with the exception of wherein any substituent containing a heterocyclic ring bears one or two oxo or thioxo substituents on said ring; and wherein R^{14} and R^{15} are as defined in claim 1 with the exception of wherein they together with the nitrogen atom to which they are attached represent a 5- or 6-membered ring and said ring bears one or two oxo or thioxo substituents; save that R^1 may represent 4-pyridon-1-yl, 4-pyridon-1-yl-C_{1-4} alkyl, 4-pyridon-1-yl-C_{2-4} alkoxy, 4-pyridon-1-yl-C_{2-4} alkylamino, 2-oxopyrrolidin-1-yl or 2,5-dioxopyrrolidin-1-yl.

3. A compound as claimed in claim 1 or claim 2 wherein X is N.

4. A compound as claimed in any one of claims 1 to 3 wherein Y is NR^b, $NR^b(CH_2)$, or $(CH_2)NR^b$, preferably Y is NR^b and R^b is preferably hydrogen or methyl.

5. A compound as claimed in any one of claims 1 to 4 wherein R'' is a 5- or 6-membered heterocyclic ring as defined in claim 1, optionally substituted by one or more R^1 groups selected from the group comprising amino, hydrogen, halogen, hydroxy, hydroxy-C_{1-4} alkyl, formyl, carboxy, cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylsulphinyl, C_{1-8} alkylsulphonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, dioxolanyl or hydroxy-C_{1-4} alkanoyl-(C_{1-4} alkyl)-amino.

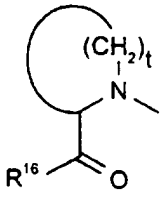
6. A compound as claimed in any one of claims 1 to 4 wherein n is 0 and each R^1 is selected from the group comprising amino, hydrogen, halog n, hydroxy,

hydroxy-C_{1-4} alkyl, formyl, carboxy, cyano, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, C_{1-8} alkylsulphinyl, C_{1-8} alkylsulphonyl, C_{1-4} alkylamino, C_{1-4} dialkylamino, dioxolanyl, benzyloxy or hydroxy-C_{1-4} alkanoyl-(C_{1-4} alkyl)-amino.

7. A compound as claimed in claim 6 wherein p is 1 and R^1 is selected from the group comprising amino, C_{1-4} alkylamino, diC_{1-4} alkylamino, especially diC_{1-4} alkylamino, most especially dimethylamino or methylethylamino.

8. A compound as claimed in any one of claims 1 to 4 wherein R" is a 5- or 6-membered heterocyclic ring as defined in claim 1 substituted with an R^1 group selected from M^1-M^2-M^3-M^4, M^1-M^5 or M^1-M^2-$M^{3'}$-M^6 as defined in claim 1 or claim 2; and p = 0.

9. A compound as claimed in any one of claims 1 to 4 or 8 wherein M^1 represents CH_2 , CO, CH_2CH_2 or CH_2CO; M^2 represents NR^{12} in which R^{12} is as defined in claim 1; M^3 represents CH_2, CH_2CH_2 or propyl; $M^{3'}$ represents CH_2, ethyl, propyl, isopropyl or is absent; M^4 represents SOR^{13}, SO_2R^{13}, $NR^{12}SO_2R^{13}$, CO_2R^{13} or $CONR^{14}R^{15}$ in which R^{12} and R^{13} are defined in claim 1 and R^{14} and R^{15} each independently represent H or C_{1-4} alkyl; M^5 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} together with the nitrogen atom to which they are attached represent a 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may optionally be substituted with a C_{1-4} alkyl group; or M^5 represents a group



in which t represents 2 or 3 and R^{16} represents OH, NH_2, N(C_{1-4} alkyl)$_2$ or OC_{1-4} alkyl; more preferably R^{16} represents NH_2 or N$(CH_3)_2$; or M^5 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} each independently represent hydrogen or C_{1-4} alkyl, more preferably hydrogen, methyl, ethyl or isopropyl; and M^6 represents a group $NR^{14}R^{15}$ in which R^{14} and R^{15} each independently represent C_{1-4} alkyl, more preferably methyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached repres nt a 5- or 6-membered ring optionally containing an additional heteroatom selected from N or O, in which ring any nitrogen atom present may

optionally be substituted with a C_{1-4} alkyl group, preferably a methyl group; or M^6 represents a 5- or 6-membered heterocyclic ring system containing 1 or 2 heteroatoms selected from N or O.

10. A compound as claimed in any one of claims 1 to 4, 8 or 9 wherein M^2-M^3-M^4 represents an α-amino carboxylic acid or a methyl ester or amide thereof; or M^2-M^3-M^4 represents a β- or γ-amino sulphinic or sulphonic acid or a methyl ester thereof.

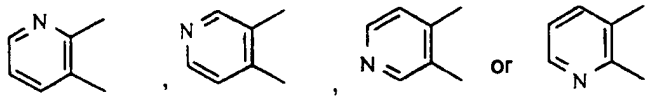
11. A compound as claimed in any one of claims 1 to 4 or 8 to 10 wherein M^2-M^3-M^4 represents a methylsulphonylethylamino, methylsulphinylethylamino, methylsulphonylpropylamino, methylsulphinylpropylamino, methylsulphonamidoethylamino, sarcosinamide, glycine, glycinamide, or glycine methyl ester group.

12. A compound as claimed in any one of claims 1 to 4, 8 or 9 wherein M^1-M^5 represents a piperazinyl-methyl, methylpiperazinyl-methyl, piperidinyl-methyl, prolinamidomethyl, N,N-dimethylprolinamido-methyl, isopropylacetamido or N-morpholinoacetamido group.

13. A compound as claimed in any one of claims 1 to 5 or 8 to 12 wherein R" is selected from the group comprising phenyl, furan, imidazole, tetrazole, triazole, pyrrolidine, piperazine, piperidine and oxadiazole.

14. A compound as claimed in any one of claims 1 to 13 wherein R^6 is benzyl, fluorobenzyl, benzyloxy, fluorobenzyloxy, pyridylmethyl, phenyl, benzenesulphonyl, phenoxy or fluorophenoxy.

15. A compound as claimed in any one of claims 1 to 14 wherein A represents



16. A compound as claimed in claim any one of claims 1 to 15 wherein U represents an indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group.

17. A compound as claimed in any one of claims 1 to 16 wherein the optional substituents for the carbocyclic or heterocyclic moiety and also for other optionally substituted groups include hydroxy, halogen, trifluoromethyl, trifluoromethoxy, nitro, amino, cyano, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, carboxylate and C_{1-4} alkoxy carboxyl.

18. A compound as claimed in any one of claims 1 to 4 wherein X represents N; A represents a pyridine ring; and either (a) p is 0; n is 1; and the group R'' is in the 6-position of the pyridopyrimidine ring system or (b)

n is 0; p is 1; and the group R^1 is in the 6-position of the pyridopyrimidine ring system.

19. A compound of formula (I) or a salt or solvate thereof as claimed in any one of claims 1 to 5 or 18 wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring; R'' represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, optionally substituted by one or more R^1 groups selected from halo, C_{1-4} alkyl, carboxy, formyl, hydroxy-C_{1-4} alkyl, 1,3-dioxolan-2-yl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy-C_{1-4} alkanoyl(C_{1-4} alkyl)amino, C_{1-4} alkylamino-C_{1-4} alkyl or di(C_{1-4} alkyl)amino-C_{1-4} alkyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indolyl, benzimidazolyl or indazolyl, more preferably indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

20. A compound of formula (I) or a salt or solvate thereof as claimed in any one of claims 1 to 4, 8 or 18 wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring, R'' represents furan, thiophene, pyrrole, pyridine, pyrimidine, pyrazine, imidazole, oxazole, isoxazole, oxadiazole, tetrazole, triazole, dioxolane or a partially or fully hydrogenated derivative of any of these groups, optionally substituted with an R^1 group selected from methylsulphonylethylaminomethyl, methylsulphonylethylamino-carbonyl,

methylsulphinylethylamino-methyl, methylsulphinylethylamino-carbonyl, methylsulphonylpropylamino-methyl, methylsulphinylpropylamino-methyl, methylsulphonylpropyamino-carbonyl, methylsulphinylpropylamino-carbonyl, methylsulphonylethyl-(methylamino)-methyl, methylsulphonylethyl-(methylamino)-carbonyl, methylsulphinylethyl-(methylamino)-methyl, methylsulphinylethyl-(methylamino)-carbonyl, methylsulphonylpropyl-(methylamino)-methyl, methylsulphinylpropyl-(methylamino)-methyl, methylsulphonylpropyl-(methylamino)-carbonyl, methylsulphinylpropyl-(methylamino)-carbonyl, methylsulphonamidoethylamino-methyl, methylsulphonamidopropylamino-methyl, sarcosinamidomethyl, glycinylmethyl, glycinamidomethyl, glycinylmethyl methyl ester, acetylaminoethylaminomethyl, piperazinylmethyl, methylpiperazinylmethyl, piperidinylmethyl, N-(prolinamido)methyl, (N,N-dimethyl-prolinamido)methyl, pyridylaminomethyl, cyclopropylaminomethyl, N-(piperidin-4-yl)-N-methylaminomethyl, N,N-dimethylaminoprop-2-ylaminomethyl, N-(2-dimethylaminoethyl)-N-ethylaminomethyl, isopropylacetamido, N-morpholinylacetamido or tetrahydrofuranomethylaminomethyl and optionally further substituted by one or more C_{1-4} alkyl groups; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indolyl, benzimidazolyl or indazolyl, more preferably indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

21. A compound of formula (I) or a salt or solvate thereof as claimed in any one of claims 1 to 4, 6, 7 or 18 wherein X represents N; Y represents NR^a wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring; n is 0; each R^1 group is selected from hydrogen, halo, C_{1-4} alkyl, carboxy, formyl, hydroxy-C_{1-4} alkyl, 1,3-dioxolan-2-yl, benzyloxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy-C_{1-4} alkanoyl(C_{1-4} alkyl)amino, C_{1-4} alkylamino-C_{1-4} alkyl, di(C_{1-4} alkyl)amino-C_{1-4} alkyl, methylsulphonylethylaminomethyl, methylsulphonylethylamino-carbonyl, methylsulphinylethylamino-methyl, methylsulphinylethylamino-carbonyl, methylsulphonylpropylamino-methyl, methylsulphinylpropylamino-methyl, methylsulphonylpropyamino-carbonyl, methylsulphinylpropylamino-carbonyl, methylsulphonylethyl-(methylamino)-methyl, methylsulphonylethyl-(methylamino)-carbonyl, methylsulphinylethyl-(methylamino)-methyl, methylsulphinylethyl-(methylamino)-carbonyl, methylsulphonylpropyl-(methylamino)-methyl,

methylsulphinylpropyl-(methylamino)-methyl, methylsulphonylpropyl-(methylamino)-carbonyl, methylsulphinylpropyl-(methylamino)-carbonyl, methylsulphonamidoethylamino-methyl, methylsulphonamidopropylamino-methyl, sarcosinamidomethyl, glycinylmethyl, glycinamidomethyl, glycinylmethyl methyl ester, acetylaminoethylaminomethyl, piperazinylmethyl, methylpiperazinylmethyl, piperidinylmethyl, N-(prolinamido)methyl, (N,N-dimethyl-prolinamido)methyl, pyridylaminomethyl, cyclopropylaminomethyl, N-(piperidin-4-yl)-N-methylaminomethyl, N,N-dimethylaminoprop-2-ylaminomethyl, N-(2-dimethylaminoethyl)-N-ethylaminomethyl, isopropylacetamido, N-morpholinylacetamido or tetrahydrofuranomethylaminomethyl; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indolyl, benzimidazolyl or indazolyl, more preferably indazolyl; and R^6 represents phenyl, benzyl, α-methylbenzyl, fluorobenzyl, benzenesulphonyl, phenoxy, fluorophenoxy, benzyloxy or fluorobenzyloxy.

22. A compound as claimed in claim 19 or claim 20 wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring; R'' represents a furan, imidazole, triazole, oxadiazole, pyrrolidine, piperidine or piperazine ring, optionally substituted by one or more R^1 groups selected from 1,3-dioxolan-2-yl, formyl, carboxy, C_{1-4}-alkyl, prolinamidomethyl, isopropylacetamido, N-morpholinylacetamido, methylsulphonylethylaminomethyl or methylsulphonylethylaminocarbonyl; p is 0; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indazolyl, indolyl or benzimidazolyl, more preferably indazolyl; and R^6 represents benzyl, fluorobenzyl, pyridylmethyl or benzenesulphonyl.

23. A compound as claimed in claim 21 wherein X represents N; Y represents NR^a, wherein R^a is hydrogen or C_{1-4} alkyl; A represents a pyridine ring; n is 0; each R^1 group is selected from hydrogen, halo, benzyloxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino or hydroxy-C_{1-4} alkanoyl-(C_{1-4} alkyl)-amino, more preferably dimethylamino; R^2 represents hydrogen; R^4 represents hydrogen or methyl; U represents indazolyl, indolyl or benzimidazolyl, more preferably indazolyl; and R^6 represents benzyl, fluorobenzyl, pyridylmethyl or benzenesulphonyl.

24. A comound as claimed in claim 1 or claim 2 selected from:

(1-Benzyl-1H-indazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N4-(1-Benzyl-1H-indazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
(1-Benzyl-1H-indazol-5-yl)-6-(N-(2-hydroxyethyl)-N-methylamino)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(pyrido[3,4-d]pyrimidin-4-yl)-amine;
(2-Benzyl-1H-benzimidazol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N4-(1-Benzyl-1H-indol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(2-Benzyl-1H-benzimidazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]-pyrimidine-4,6-diamine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-[1,3-dioxolan-2-yl]-furan-2-yl)-pyrido[3,4-d]-pyrimidin-4-yl)-amine;
5-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-carbaldehyde;
(2S)-1-(5-(4-(1-Benzyl-1H-indazol-5-ylamino)-6-pyrido[3,4-d]pyrimidin-6-yl)-furan-2-ylmethyl)-pyrrolidine-2-carboxylic acid amide;
(1-Benzyl-1H-indazol-5-yl)-(6-(3-methyl-3H-imidazol-4-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N6,N6-Dimethyl-N4-(1-pyridin-2-ylmethyl-1H-indazol-5-yl)-pyrido[3,4-d]pyrimidine-4,6-diamine;
N6,N6-Dimethyl-N4-(1-pyridin-3-ylmethyl-1H-indazol-5-yl)-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-Benzyl-3-methyl-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-(2-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-(4-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-Benzenesulphonyl-1H-indol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(3-Benzenesulphonyl-1H-indol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
(1-Benzyl-1H-indazol-5-yl)-(6-imidazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,4-triazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;

(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,3-triazol-2-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(1,2,3-triazol-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-pyrrolidin-1-yl-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-piperidin-1-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
N4-(1-Benzyl-1H-indazol-5-yl)-N6-ethyl-N6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
2-(4-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-piperazin-1-yl)-N-isopropyl-acetamide;
2-(4-(4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido[3,4-d]pyrimidin-6-yl)-piperazin-1-yl)-1-morpholin-4-yl-ethanone;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-(6-(5-methyl-1,3,4-oxadiazol-2-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indol-5-yl)-(6-chloro-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(4-methyl-piperazin-1-yl)-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazolyl-5-yl)-(6-benzyloxy-pyrido[3,4-d]pyrimidin-4-yl)-amine;
(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesuphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido-[3,4-d]pyrimidin-4-yl)-amine;
5-[4-(1-Benzyl-1H-indazol-5-ylamino)-pyrido-[3,4-d]pyrimidin-6-yl]-furan-2-carboxylic acid;
5-[4-(1-benzyl-1H-indazol-5-ylamino)-pyrido-[3,4-d]pyrimidin-6-yl]-furan-2-carboxylic acid 2-methanesulphonyl-ethylamide;
*N*4-(1-Benzyl-1H-indazol-5-yl)-*N*6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine; N4-[1-(4-Hydroxybenzyl)-1H-indazol-5-yl)-*N*6,*N*6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

25. A compound as claimed in claim 24 selected from:
N4-(1-Benzyl-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-(3-Fluoro-benzyl)-1H-indazol-5-yl)-N6,N6-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
N4-(1-Benzyl-1H-indazol-5-yl)-N6-ethyl-N6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine;

(1-Benzyl-1H-indazol-5-yl)-(6-(5-((2-methanesuphonyl-ethylamino)-methyl)-furan-2-yl)-pyrido-[3,4-d]pyrimidin-4-yl)-amine;
N4-(1-Benzyl-1H-indazol-5-yl)-N6-methyl-pyrido[3,4-d]pyrimidine-4,6-diamine;
and salts or solvates thereof, particularly pharmaceutically acceptable salts or solvates thereof.

26. A pharmaceutical formulation comprising at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

27. A pharmaceutical formulation as claimed in claim 26 in unit dosage form and containing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in an amount of from 70 to 700mg.

28. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

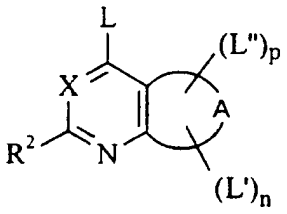
29. The use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in the treatment of disorders mediated by aberrant protein tyrosine kinase activity.

30. The use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in the treatment of cancer and malignant tumours.

31. The use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in the treatment of psoriasis.

32. A method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity which comprises administering to the human or animal subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

33. A process for the preparation of a compound of formula (I) as defined in claim 1 or claim 2 which comprises the st ps:
(a) the reaction of a compound of formula (II)

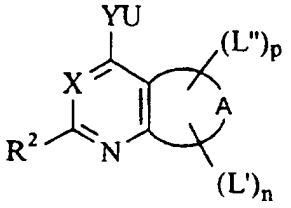


(II)

wherein A, X, n, p and R^2 are as defined in claim 1 and L, L' and L'' are suitable leaving groups, with a compound of formula (III)

UYH (III)

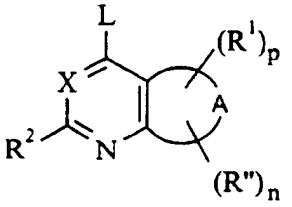
wherein U and Y are as defined above, to prepare a compound of formula (IV)



(IV)

and subsequently (b) where n is 1, reaction with an appropriate reagent to substitute the group R'' onto the ring A by replacement of the leaving group L'; and (c) where p is other than 0, reaction with appropriate reagent(s) to substitute the group(s) R^1 onto the ring A by replacement of the leaving group(s) L''; and, if desired, (d) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

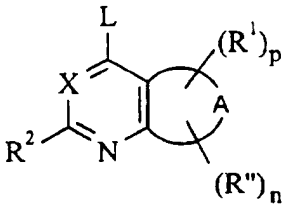
34. A process for the preparation of a compound of formula (I) as defined in claim 1 or claim 2 in which the compound of formula (II) as defined in claim 33 is reacted with the appropriate reagents to substitute the groups R'' and R^1 onto the ring A by replacement of the respective leaving groups and then the product thereby obtained of formula (V)



(V)

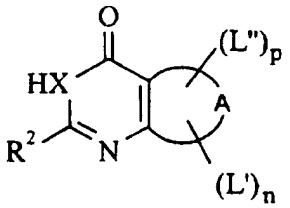
is reacted with the compound of formula (III) as defined in claim 33, followed, if desired, by conversion of the compound of formula (I) thereby obtained into another compound of formula (I).

35. A process as claimed in claim 34 wherein the compound of formula (V)



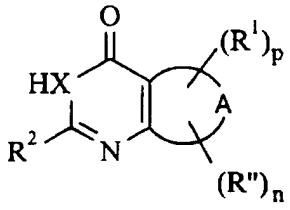
(V)

is prepared by the reaction of a compound of formula (VI)



(VI)

with appropriate reagents to substitute the group(s) R^1 and the group R'' onto the ring A to prepare a compound of formula (VII)



(VII)

and subsequent reaction to incorporate the leaving group L.

36. A process for the preparation of a compound of formula (I) as defined in claim 1 or claim 2 which comprises the steps:
(a) reacting a compound of formula (IV) as defined in claim 33 with appropriate reagent(s) to prepare a compound wherein either the group L' (when n=1) or the group(s) L'' (when p is other than 0) is(are) replaced with an appropriately functionalised group Z;

and (b) subsequently converting the group Z into the group R'' where L' has been replaced or into the group R^1 where L'' has been replaced by means of appropriate reagent(s); (c) reacting with appropriate reagents to substitute the other of R^1 and R'' onto the ring A by replacement of the remaining leaving group L'' and L'' respectively, if present; and, if desired, (d) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

37. A process for the preparation of a compound of formula (I) as defined in claim 1 or claim 2 which comprises the steps:
(a) reacting a compound of formula (II) as defined in claim 33 with appropriate reagent(s) to prepare a compound wherein either the group L' (when n=1) or the group(s) L'' (when p is other than 0) is(are) replaced with an appropriately functionalised group Z;
and (b) subsequently converting the group Z into the group R'' where L' has been replaced or into the group R^1 where L'' has been replaced by means of appropriate reagent(s); (c) reacting with appropriate reagents to substitute the other of R^1 and R'' onto the ring A by replacement of the remaining leaving group L'' and L' respectively, if present; (d) the product thereby obtained is reacted with the compound of formula (III) as defined in claim 33; and, if desired, (e) subsequently converting the compound of formula (I) thereby obtained into another compound of formula (I) by means of appropriate reagents.

38. Compounds of formulae (II), (III), (IV), (V), (VI) and (VII) as defined in any one of claims 33 to 35 wherein X, Y, U, A, R^1, R^2, n and p are as defined in any one of claims 1 to 23.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/EP 97/03674

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/505 C07D209/08 C07D231/56 C07D401/06
C07D235/08 //(C07D471/04,239:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 95 19774 A (WARNER-LAMBERT) 27 July 1995 see claim 1 ---	1,26
X	FR 5 600 M (INSTITUT DE RECHERCHE SCIENTIFIQUE) 8 January 1968 see page 4, column 2, line 7 - line 28 ---	38
X	D.L. BOGER ET AL.: "Regiocontrolled nucleophilic addition to selectively activated p-quinone diimines: alternative preparation of a key intermediate employed in the preparation of the CC-1065 left-hand subunit" JOURNAL OF ORGANIC CHEMISTRY., vol. 55, no. 4, 1990, EASTON US, pages 1379-1390, XP002044433 see page 1387, column 1, line 14 - line 22 --- -/--	38

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

4

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 1997	04. 11. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 97/03674

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 13771 A (GLAXO) 17 April 1997 see page 25, lines 4 - 20; page 31, lines 27 - 29 and page 32, lines 1-3 ---	38
P,X	WO 97 18212 A (PHARMACIA) 22 May 1997 see claims 1,4 -----	1,26

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ational application No.
PCT/EP 97/03674

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos..
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 32
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

On grounds of Article 6 and 17.2a (ii) of the PCT (conciseness of claims) and of the Guidelines for Examination in the EPO, Part B, Chapter III, 2.2 (economic reasons) the search has been restricted to a generalization of the preparation examples disclosed in the description.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. .onal Application No
PCT/EP 97/03674

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9519774 A	27-07-95	US 5654307 A	05-08-97
		AU 1731495 A	08-08-95
		AU 1833495 A	08-08-95
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		NO 973198 A	09-07-97

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 413/06, A61K 31/445 C07D 498/04, 401/06, 417/06 C07D 261/20, 413/12, 211/32	A1	**(11) International Publication Number:** WO 92/17475 **(43) International Publication Date:** 15 October 1992 (15.10.92)

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(63) Related by Continuation
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Filed on 28 March 1991 (28.03.91)

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(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

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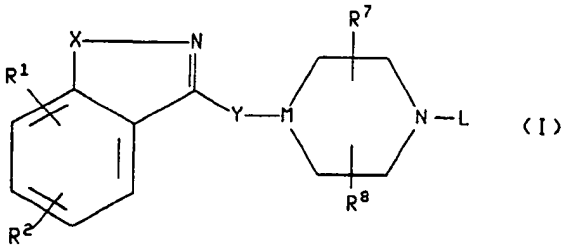
(54) Title: HETEROCYCLIC-CYCLIC AMINE DERIVATIVES



(I)

(57) Abstract

Compounds of formula (I) wherein R^1, R^2, R^7, R^8, X, Y, M and L are defined as below. The compounds of formula (I) are cholinesterase inhibitors and are useful in enhancing memory in patients suffering from dementia and Alzheimer's disease.

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HETEROCYCLIC-CYCLIC AMINE DERIVATIVES

Background of the Invention

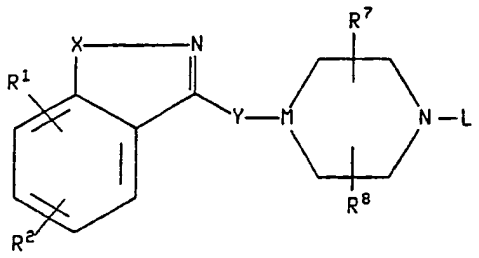
The present invention relates to heterocyclic-cyclic amine derivatives of the formula I below, and pharmaceutically acceptable salts of such compounds. The compounds of formula I are cholinesterase inhibitors and are useful in enhancing memory in patients suffering from dementia and Alzheimer's disease.

Alzheimer's disease is associated with degeneration of cholinergic neurons in the basal forebrain that play a fundamental role in cognitive functions, including memory. Becker et al., Drug Development Research, 12, 163-195 (1988). As a result of such degeneration, patients suffering from the disease exhibit a marked reduction in acetylcholine synthesis, choline acetyltransferase activity, acetylcholinesterase activity and choline uptake.

It is known that acetylcholinesterase inhibitors are effective in enhancing cholinergic activity and useful in improving the memory of Alzheimer's patients. By inhibiting acetylcholinesterase enzyme, these compounds increase the level of the neurotransmitter acetylcholine, in the brain and thus enhance memory. Becker et al., supra, report that behavioral changes following cholinesterase inhibition appear to coincide with predicted peak levels of acetylcholine in the brain. They also discuss the efficacy of the three known acetylcholinesterase inhibitors physostigmine, metrifonate, and tetrahydroaminoacridine.

Summary of the Invention

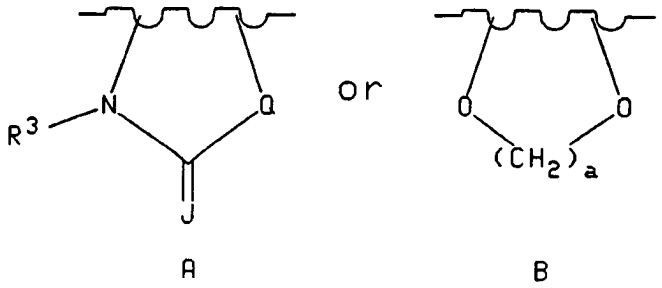
The present invention relates to compounds of the formula



(I)

wherein R^1 and R^2 are independently selected from hydrogen, (C_1-C_6)alkoxy, benzyloxy, phenoxy, hydroxy, phenyl, benzyl, halo, nitro, cyano, COR^5, $-COOR^5$, $-CONHR^5$, $-NR^5R^6$, $-NR^5COR^6$, $-OCONR^5R^6$, $-NHCOOR^5$, (C_1-C_6)alkyl optionally substituted with from 1 to 3 fluorine atoms; SO_pCH_2-phenyl or $SO_p(C_1-C_6)$alkyl, wherein p is 0, 1 or 2; pyridylmethyloxy or thienylmethyloxy; 2-oxazolyl, 2-thiazolyl and benzenesulfonamide; wherein the phenyl moieties of said phenoxy, benzyloxy, phenyl, benzyl and benzenesulfonamide groups, the pyridyl and thienyl moieties of said pyridylmethyloxy or thienylmethyloxy and the oxazolyl and thiazolyl moieties of said 2-oxaxolyl and 2-thiazolyl may optionally be substituted with 1 or 2 substituents independently selected from halo, (C_1-C_4)alkyl, trifluoromethyl, (C_1-C_4)alkoxy, cyano, nitro and hydroxy.

or R^1 and R^2, when attached to adjacent carbon atoms and when X is oxygen, sulfur or NR^4 wherein R^4 is hydrogen or (C_1-C_4 alkyl) may form, together with the carbon atoms to which they are attached, a group of the formula



A B

wherein J is oxygen, sulfur or NR^4, "a" is 1 or 2, R^3 is hydrogen or (C_1-C_6)alkyl and Q is oxygen, sulfur, NH, $CHCH_3$, $C(CH_3)_2$, -CH=CH-, or $(CH_2)_1$ wherein 1 is an integer from 1 to 3;

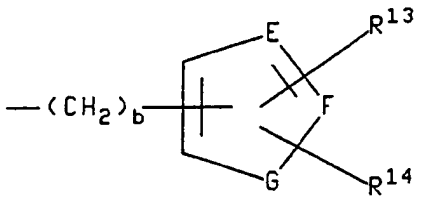
X is oxygen, sulfur, -CH=CH-, -CH=N-, -N=CH-, -N=N-, or NR^4 wherein R^4 is hydrogen or (C_1-C_4) alkyl;

Y is $-(CH_2)_m-$, $-CH=CH(CH_2)_n-$, $-NR^4(CH_2)_m-$, or $-O(CH_2)_m-$ wherein R^4 is defined as above, n is an integer from 0 to 3 and m is an integer from 1 to 3;

R^5 and R^6 are each independently selected from hydrogen, (C_1-C_6)alkyl, phenyl or benzyl, wherein the phenyl moieties of said phenyl and benzyl may optionally be substituted with 1 or 2 substituents independently selected from fluoro, chloro, bromo, iodo, (C_1-C_4) alkyl, trifluoromethyl, (C_1-C_4) alkoxy, cyano, nitro and hydroxy, or NR^5R^6 together form a 4 to 8 membered ring wherein one atom of the ring is nitrogen and the others are carbon, oxygen or nitrogen (e.g. pyrrolidinyl, piperidinyl, morpholino, piperazinyl or N-methylpiperazinyl), or NR^5COR^6 together form a 4 to 8 membered cyclic lactam ring;

M is -CH- or nitrogen;

L is phenyl, phenyl-(C_1-C_6)alkyl, cinnamyl or pyridylmethyl, wherein the phenyl moieties of said phenyl and phenyl-(C_1-C_6)alkyl may optionally be substituted with 1 to 3 substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkylcarbonyl, $-OCONR^5R^6$, $-NHCOOR^5$ or halo; or L is a group of the formula



(K)

wherein b is an integer from 1 to 4, R^{13} and R^{14} are independently selected from hydrogen, (C_1-C_4) alkyl, halo and phenyl, E and F are independently selected from -CH- and nitrogen, and G is oxygen, sulfur or NR^4 wherein R^4 is defined as above, with the proviso that when E and F are both nitrogen, one of R^{13} and R^{14} is absent; and

R^7 and R^8 are independently selected from hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyl and (C_1-C_6)alkoxy, with the proviso that said (C_1-C_6)alkoxy is not attached to a carbon that is adjacent to a nitrogen.

This invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. Examples of such pharmaceutically acceptable acid addition salts are the salts of hydrochloric acid, p-toluenesulfonic acid, maleic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, di-p-toluoyl tartaric acid, and mandelic acid.

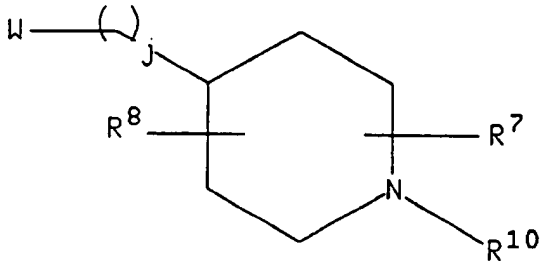
This invention also relates to a pharmaceutical composition for inhibiting cholinesterase comprising a compound of the formula I or a pharmaceutically acceptable acid addition salt thereof, and a pharmaceutically acceptable carrier.

This invention also relates to a method for inhibiting cholinesterase in a mammal comprising administering to a mammal an amount of a compound of the formula I or a pharmaceutically acceptable acid addition salt thereof effective in inhibiting cholinesterase.

This invention also relates to a method for enhancing memory or treating or preventing Alzheimer's disease in a

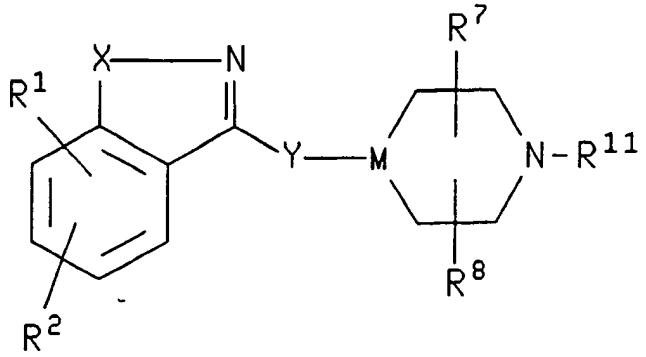
mammal comprising administering to a mammal an amount of a compound of the formula I or a pharmaceutically acceptable acid addition salt thereof effective in enhancing memory or treating or preventing Alzheimer's disease.

This invention also relates to compounds of the formula



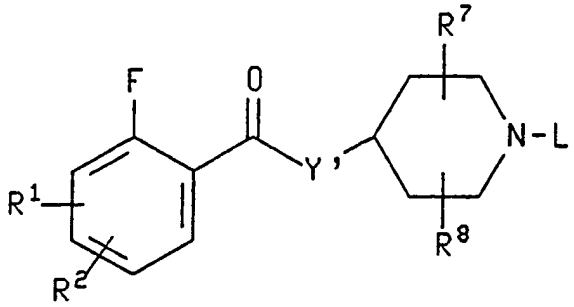
wherein W is a leaving group; j is an integer from 0 to 2; R^{10} is a nitrogen protecting group; and R^7 and R^8 are independently selected from hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylcarbonyl and (C_1-C_6) alkoxy, with the proviso that said (C_1-C_6) alkoxy is not attached to a carbon that is adjacent to a carbon that is adjacent to a nitrogen. These compounds are useful as intermediates in the synthesis of compounds of the formula I.

This invention also relates to compounds of the formula



wherein R^1, R^2, R^7, R^8, X, Y and M are as defined above and R^{11} is hydrogen or a nitrogen protecting group. These compounds are useful as intermediates in the synthesis of compounds of the formula I.

This invention also relates to compounds of the formula:



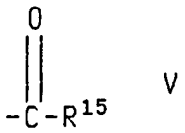
wherein R^1, R^2, R^7, R^8 and L are as defined above and Y' is $-CH=CH-(CH_2)_n-$ or $-(CH_2)_m-$. These compounds are useful as intermediates in the sythesis of compounds of the formula I.

The term "mammal", as used herein, includes humans.

The term "halo", as used herein, includes chloro, bromo, iodo or fluoro.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched, or cyclic moieties or combinations thereof.

The term "(C_1-C_4) alkylcarbonyl", as used herein, refers to a substituent of the formula



V

wherein R^{15} is (C_1-C_4) alkyl.

The term "(C_1-C_4) alkoxycarbonyl", as used herein, refers to a substituent of the formula V above, wherein R^{15} is (C_1-C_4) alkoxy.

The term "(C_1-C_6) alkoxycarbonyl", as used herein, refers to a substituent of the formula V above, wherein R^{15} is (C_1-C_6) alkoxy.

The term "(C_1-C_6)alkylcarbonyl", as used herein, refers to a substituent of the formula V above, wherein R^{15} is (C_1-C_6)alkyl.

Preferred compounds of this invention are compounds of the formula I wherein X is oxygen or sulfur, Y is $-CH_2-$, $-CH_2-CH_2-$, M is -CH- and L is benzyl, R^1 and R^2 are (C_1-C_6)alkyl, (C_1-C_6)alkoxy, NR^5R^6, or NR^5COR^6, R^3 is hydrogen or (C_1-C_6)alkyl, J is oxygen or sulfur and Q is $CH(CH_3)$, $CH(CH_3)_2$, -CH=CH or $(CH_2)_1$ and the pharmaceutically acceptable salts of such compounds.

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5-Methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5,6-Dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

5-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

7-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Acetamido-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

6-Amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Benzamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

6-Benzenesulfonamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-(4-Morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

1-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-isoquinoline;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisothiazole;

4-[2-[1-(Phenylmethyl)-4-piperidnyl]ethyl]-1,3-quinazoline;

6-Hydroxy-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Bromo-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Cyano-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Carboxamide-3-[2-[1-(phenylmethyl)-4-piperidyl]-ethyl]-1,2-benzisoxazole;

3-[(1-Phenylmethyl-4-piperidyl)methoxy]-1,2-benzisoxazole;

3-[(1-Phenylmethyl-4-piperidyl)methylamino]-1,2-benzisoxazole;

3-[2-(1-Phenylmethyl)-4-piperidyl)ethylamino]-1,2-benzisoxazole;

3-[3-[1-(Phenylmethyl)-4-piperidyl]propyl]-1,2-benzisoxazole;

trans-3-[2-[1-(Phenylmethyl)-4-piperidyl]ethenyl]-1,2-benzisoxazole;

3-[2-[1-(Phenylmethyl)-4-piperazinyl]ethyl]-1,2-benzisoxazole;

5,7-Dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-7-ethyl-3-[2[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(2-chloro-5-thiophenemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(2-methyl-4-thiazolemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(3-Bromophenylmethyl)-4-piperidinyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(4-Bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]-propyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-5,6,8-trihydro-7H-isoxazolo[4,5-g]quinolin-7-one;

6,8-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one;

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-6H-pyrrolo[5,4-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1H-indazole;

and the pharmaceutically acceptable salts of such compounds.

Examples of other compounds of the formula I are:

6-Phenylamino-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

6-(2-Thiazolyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

6-(2-Oxazolyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

6-Pyrrolidinyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

6-Piperidinyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

5,7-Dihydro-5,5-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-7-n-propyl-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-7-i-propyl-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-6-phenylmethylsulfone-1,2-benzisoxazole;

1-Methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1H-indazole; and

3-[1-Phenylmethyl-4-piperidinyl)methyl]-1,2-benzisoxazole.

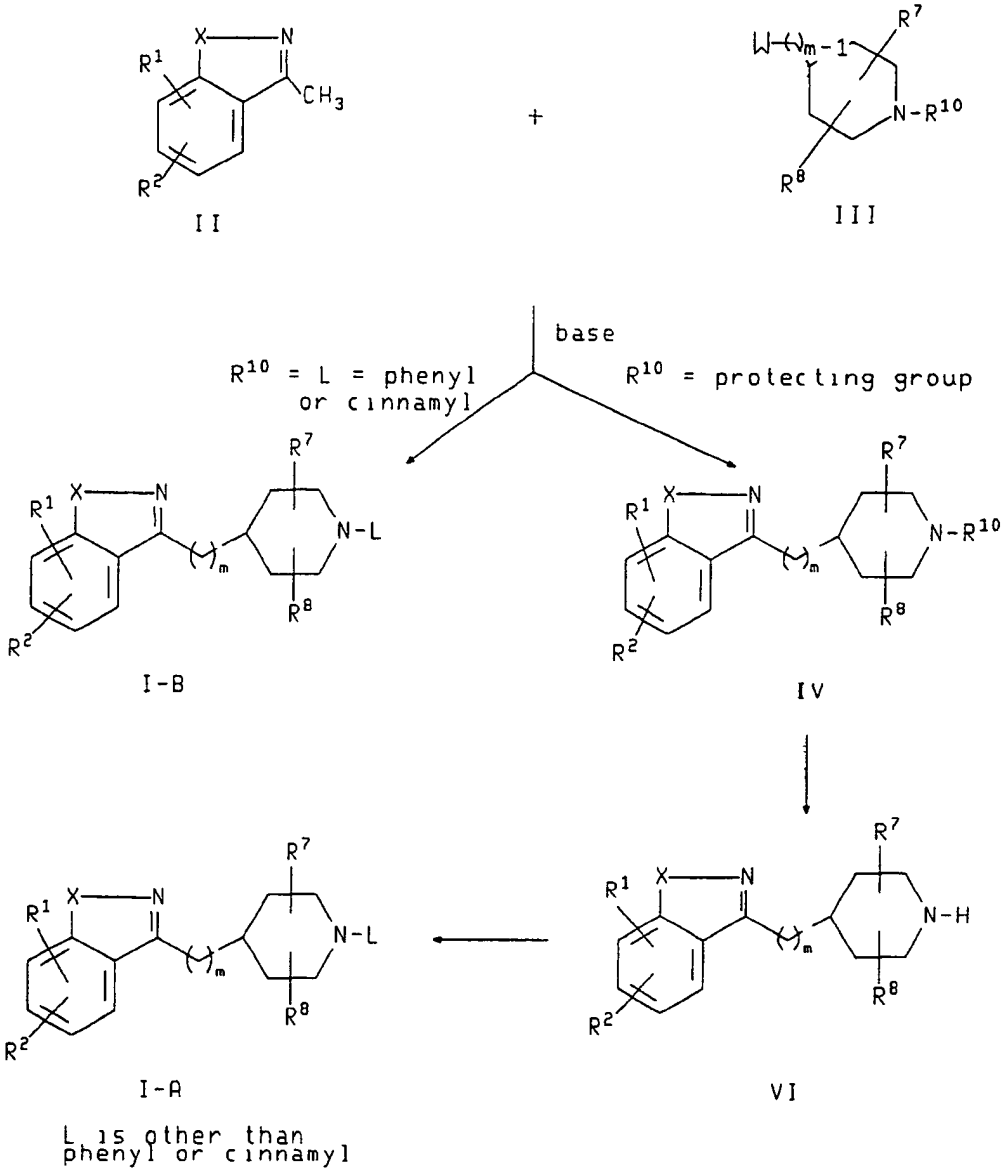
The compounds of formula I may have optical centers and may therefore occur in different isomeric forms. The invention includes all stereoisomers of such compounds of formula I, including mixtures thereof.

Detailed Description of the Invention

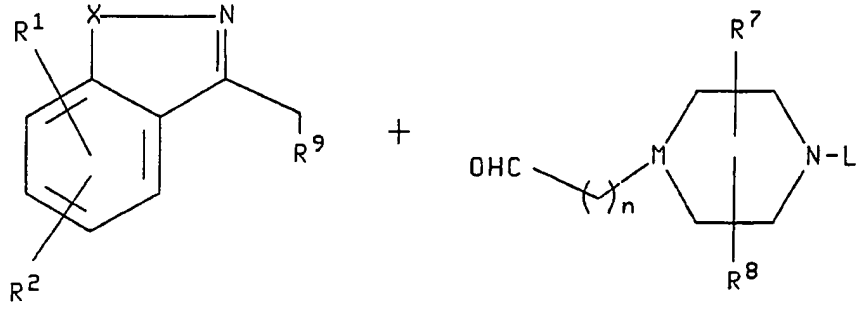
The preparation of compounds having the formula I and certain of the starting materials used in their synthesis is illustrated in the following reaction schemes. Except where otherwise stated, in the reaction schemes and discussion that follow, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{13}, R^{14}, E, G, X, Y, M, L, a, b, l, m, n, p, and structures I, A, B, and K are defined as above.

All articles, books, patents and patent applications cited in the following discussion are incorporated herein by reference.

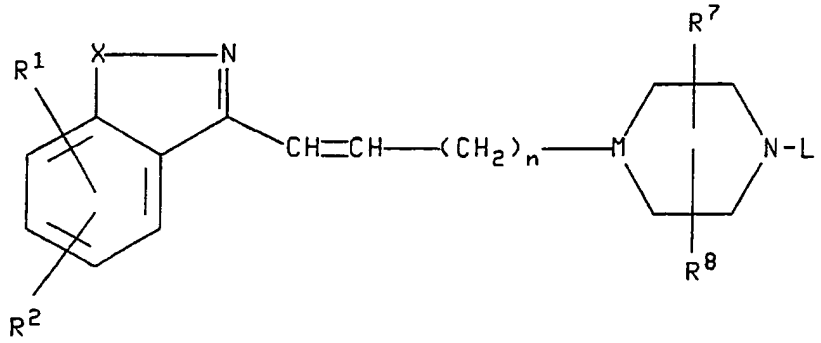
SCHEME 1


II
III
base
R10 = L = phenyl or cinnamyl
R10 = protecting group
I-B
IV
VI
I-A
L is other than phenyl or cinnamyl

SCHEME 2

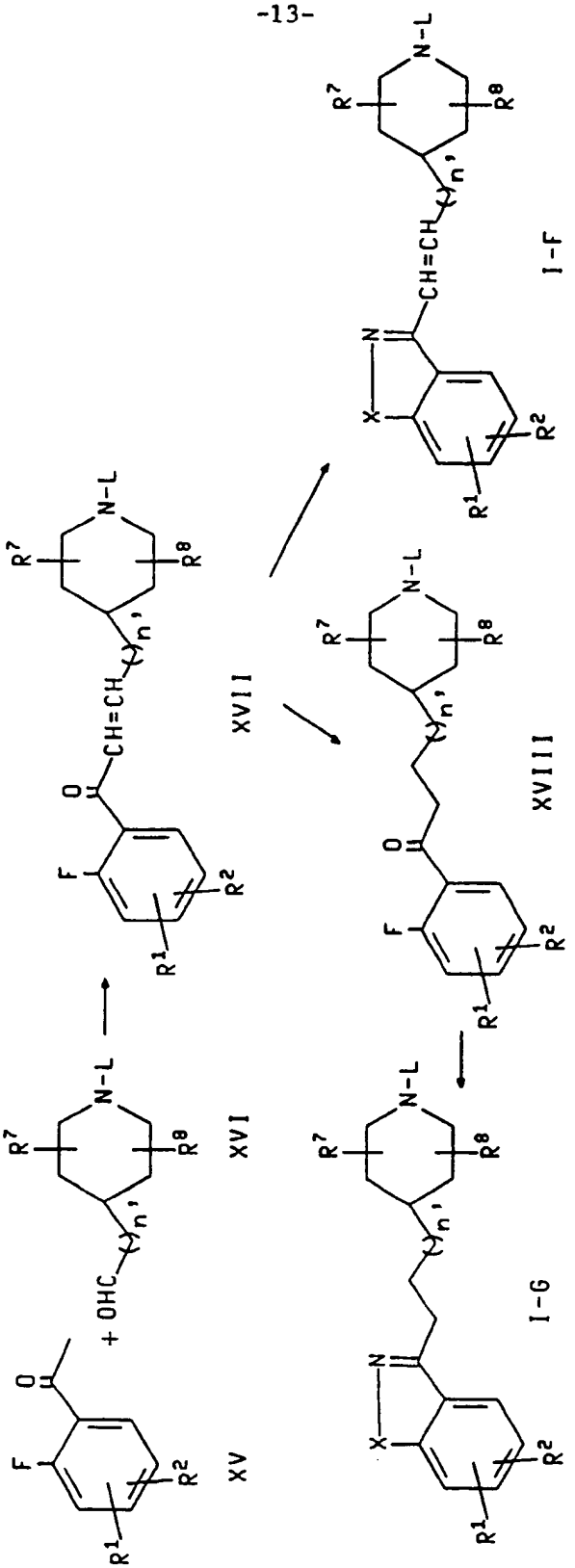


IX X

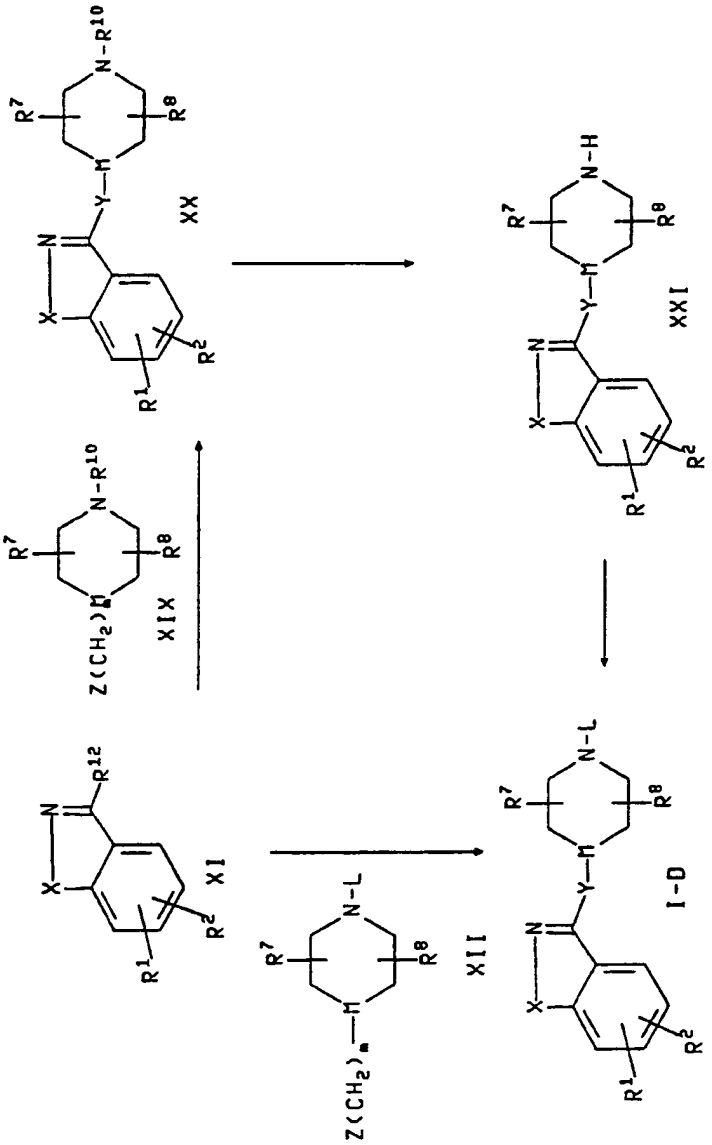


I-C

SCHEME 2'



SCHEME 3



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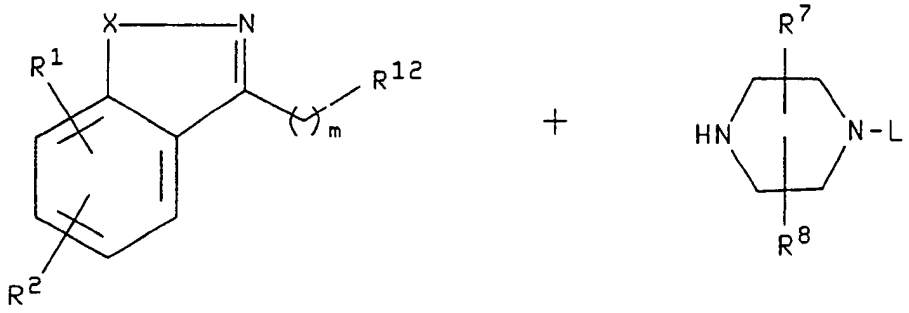
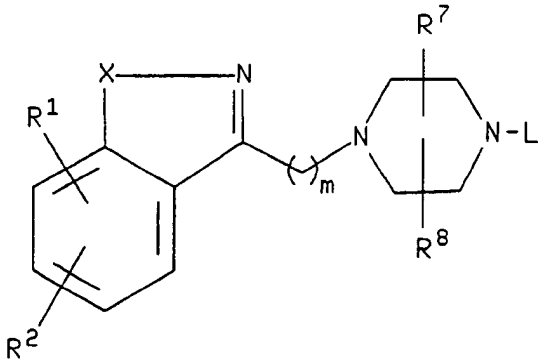
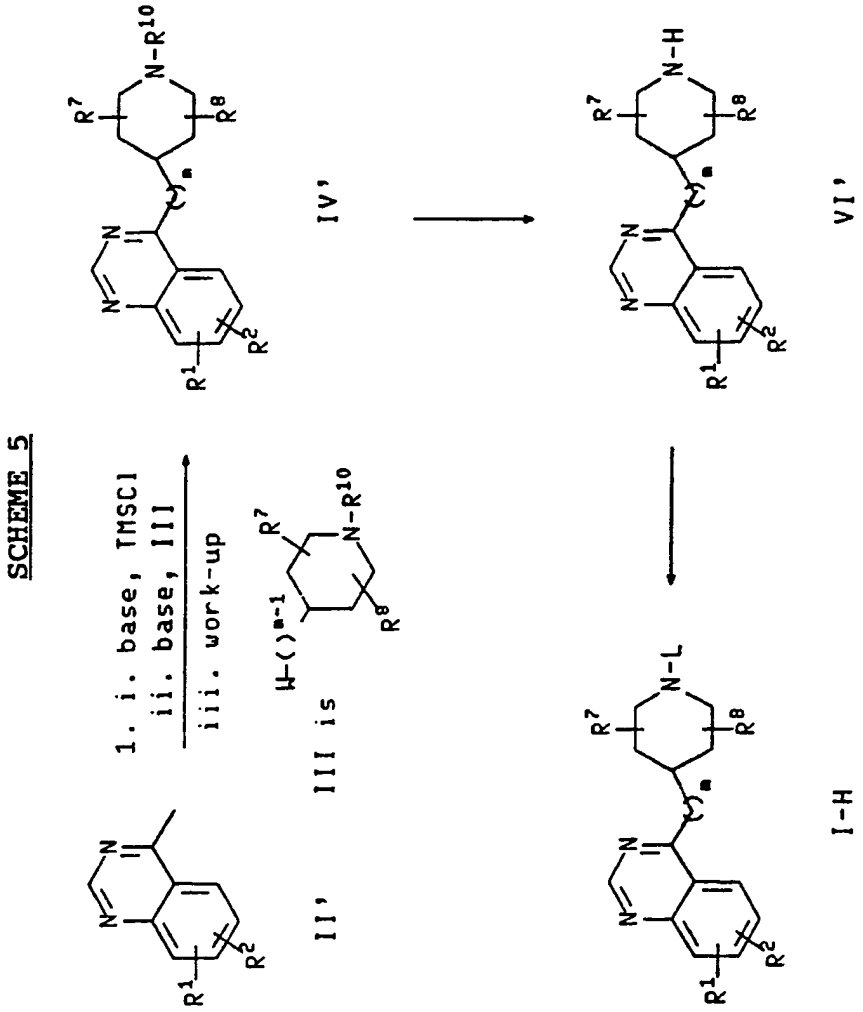


XIII XIV

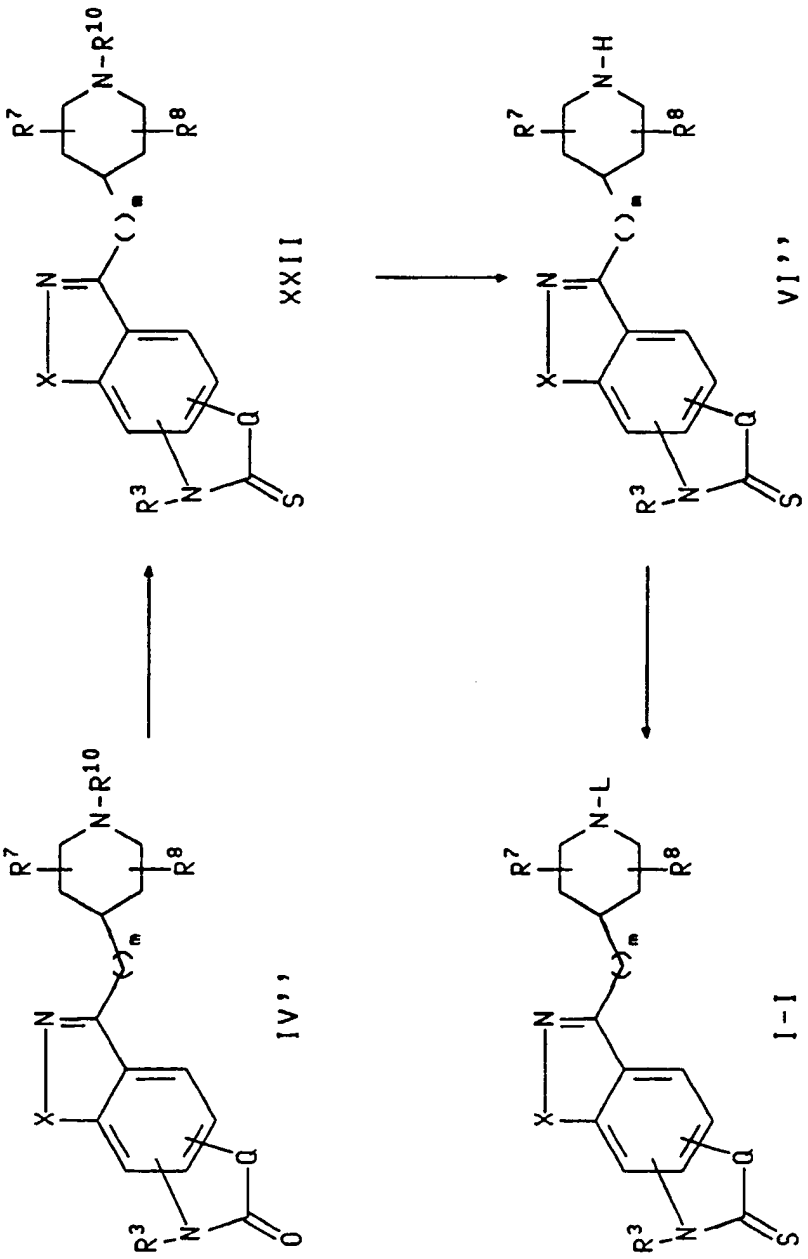


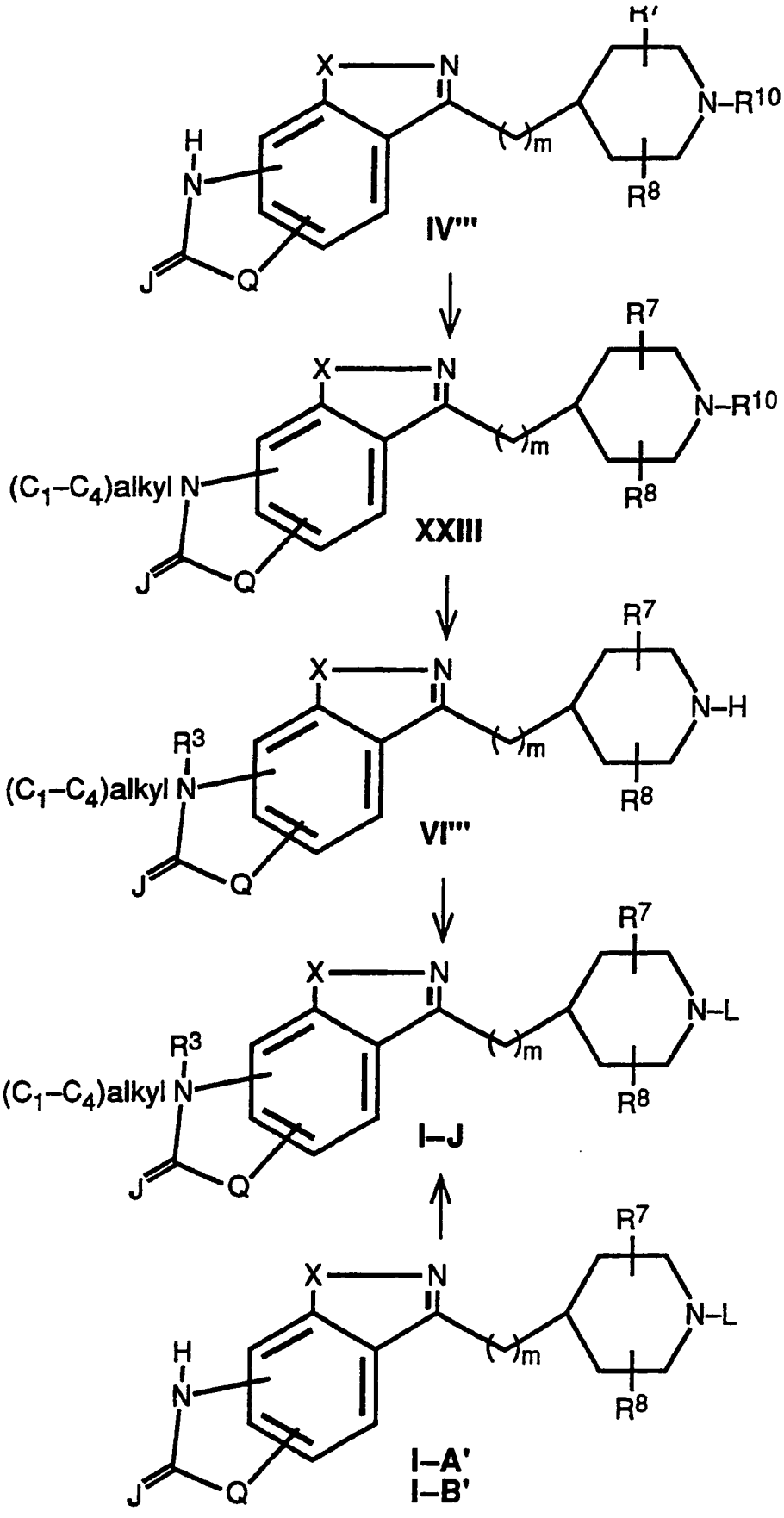
I-E

SCHEME 5



SCHEME 6




IV'''
XXIII
VI'''
I-J
I-A'
I-B'

The preparation of compounds of the formula I wherein Y is $-(CH_2)_m$ and M is -CH- is illustrated in scheme 1. These compounds are designated in scheme 1 and hereinafter referred to as compounds of the formula I-A (those wherein L is phenyl-(C_1-C_6)alkyl, pyridylmethyl or a group of the formula K) and compounds of the formula I-B (those wherein L is phenyl or cinnamyl).

Referring to scheme 1, compounds of the formula I-A may be prepared by deprotonating a compound of the formula II with a base in the presence of, or followed by the addition of an alkylating agent of the formula III wherein R^{10} is a nitrogen protecting group and W is a leaving group. When R^{10} is a nitrogen protecting group, this reaction produces an intermediate of the formula IV. This intermediate is then deprotected to yield a secondary piperidine of the formula VI as a free base or a salt of the free base, after which such free base or salt is alkylated with a compound of the formula WL, wherein W is defined as above and L is phenyl-(C_1-C_6)alkyl, pyridylmethyl or a group of the formula K.

Examples of suitable leaving groups (W) are mesylate, tosylate, chloride, iodide and bromide. Examples of suitable nitrogen protecting groups (R^{10}) are amides such as N-formyl and N-acetyl and carbamates such as t-butoxycarbamate (BOC). The preferred nitrogen protecting group is BOC. Appropriate bases for use in the preparation of compounds of the formula IV include strong bases such as lithium diisopropylamide (LDA), n-butyllithium, s-butyllithium, and lithium (or sodium or potassium) hexamethyldisilazide (LiHMDS, NaHMDS, or KHMDS). LDA and s-butyllithium are preferred.

The reaction of a compound of formula II with a compound of formula III is generally carried out in a polar, aprotic solvent such as diethyl ether, 1,2-dimethoxyethane, or tetrahydrofuran (THF). Temperatures may range from about -78°C to about 30°C. This reaction is preferably conducted in THF at about -78°C.

Usually, compounds of the formula II are deprotonated in the presence of a compound of formula III. However, in cases where the compound of formula II has more than one acidic proton, it is preferable to carry out the deprotonation step first followed by the immediate and rapid addition of the alkylating agent of formula III.

The protecting group (R^{10}) can be removed from compounds of the formula IV to form the corresponding compounds of formula VI by methods known to those skilled in the art. For example, when R^{10} is BOC or another carbamate, it can be removed with an acid such as hydrogen bromide (gas or aqueous), hydrogen chloride (gas or aqueous) or trifluoroacetic acid. In the case of trifluoroacetic acid, a t-butyl cation scavenger such as thioanisole may be added. When an acid is used as the deprotecting agent, an acid addition salt of the compound of formula VI is produced rather than the free base of such compound. Appropriate solvents include non-polar solvents such as methylene chloride, as well as polar solvents such as diethyl ether, ethyl acetate, dioxane, alcohols (e.g. methanol or ethanol) and water. Temperatures may range from about -20°C to about the reflux temperature of the solvent. It is preferable to use trifluoroacetic acid in methylene chloride with or without thioanisole at about 0°C.

Alternatively, when R^{10} is BOC, it can be removed with a trialkylsilyltrifluoromethanesulfonate derivative such as trimethylsilyl-, triethylsilyl-, or t-butyldimethylsilyl-trifluoromethanesulfonate in the presence of an aromatic or tertiary amine base such as 2,6-lutidine or triethylamine. Appropriate solvents for this reaction include nonpolar solvents such as methylene chloride and polar aprotic solvents such as THF, diethyl ether or DMF. Temperatures may range from about -20°C to room temperature. It is preferable to use trimethylsilyltrifluoromethane-sulfonate and 2,6-lutidine in methylene chloride at a temperature from about 0°C to about room temperature.

The intermediate secondary piperidine of the formula VI, obtained as the free base or salt as described above, is reacted with 2-10 equivalents of a base and then with an alkylating agent of the formula WL, wherein W is defined as above and L is phenyl-(C_1-C_6)alkyl, pyridylmethyl or a group of the formula K. Suitable bases include tertiary amines such as triethylamine and diisopropylethyl-amine, aromatic amines such as pyridine and dimethylaminopyridine, and metal carbonates such as sodium bicarbonate or sodium or potassium or cesium carbonate. When W is chloride, catalytic iodide (potassium iodide or tetra-n-butylammonium iodide) may be added. Appropriate solvents include non-polar solvents such as methylene chloride and polar solvents such as dimethylformamide, THF, acetontrile, acetone, dioxane, and alcohols such as methanol or ethanol. It is preferable to carry out the alkylation in the presence of triethylamine in methylene chloride at room temperature or in the presence of sodium carbonate in dimethylformamide at room temperature.

Alternatively, the intermediate secondary piperidine of formula VI, when obtained as a salt after removal of the protecting group, can be deprotonated to the free amine by dissolving or suspending it in an appropriate solvent (e.g., methylene chloride or ethyl acetate), mixing it with aqueous sodium bicarbonate or aqueous sodium or potassium hydroxide and recovering the free amine from the organic layer by conventional extraction techniques. The free amine can then be subjected to alkylation with the appropriate alkylating agent of the formula WL under the conditions described above using 1-2 equivalents of an appropriate base.

The starting materials of formula II can be prepared according to methods known in the art. When X is oxygen, the starting 3-methyl-1,2-benzisoxazoles can be prepared by procedures similar to those described by Wunsch et al., Adv. Heterocycl. Chem., 1967, 8, 277; Smalley, R.K., Adv. Heterocycl. Chem. 1981, 29, 2; and Thakar et al., Indian J. Chem. 1977, 15B, 1058. The appropriate o-hydroxy acetophenones are converted to the corresponding oximes by

reaction with hydroxylamine hydrochloride in the presence of an appropriate base such as potassium or sodium hydroxide, sodium acetate or pyridine, preferably aqueous potassium hydroxide or aqueous sodium acetate, in a polar solvent such as methanol, ethanol, or water, preferably ethanol, at a temperature from about room temperature to about 120°C. The oxime is then converted to the corresponding oxime acetate by acetylation with an appropriate acylating agent such as acetic anhydride. Temperatures for this reaction may range from about room temperature to the reflux temperature of the solvent. Temperatures between 80°C and 130°C are preferred.

Ring closure to form the benzisoxazole ring may be carried out by heating the neat oxime acetate at a temperature from about 125°C to about 200°C under atmospheric pressure or reduced pressure (e.g., from about 0.01 mm Hg to about 760 mm Hg). Ring closure is preferably accomplished by heating the oxime acetate at reflux in an appropriate base such as pyridine, or by heating the oxime acetate at a temperature of about 130°C in a polar solvent such as DMF or DMSO (dimethylsulfoxide) in the presence of several equivalents of an appropriate base such as pyridine or 2,6-lutidine.

Alternatively, ring closure can be carried out directly from the oxime by reaction with an acyl or sulfonyl chloride such as oxalyl or thionyl chloride in the presence of an aromatic amine such as pyridine (See Kalkote et al., Aust. J. Chem. 1977, 30, 1847). Suitable solvents include polar solvents such as diethyl ether or THF. Temperatures can range from about 0°C to about room temperature. Another method of closure involves treatment of the oxime with one or less equivalents of a base such as potassium hydroxide in a polar solvent such as methanol at temperatures ranging from about room temperature to about 100°C (Crabbe et al., J. Chem. Soc. Perkin Trans. I, 1973, 2220).

When X is sulfur, the starting 3-methyl-1,2-benzisothiazoles can be prepared from o-methylthio acetophenones following procedures similar to those

described above for the benzisoxazoles (See McKinnon et al., Can. J. Chem., 1988, 66, 1405 and references cited therein). The o-methylthio acetophenones are converted into the corresponding oximes and ring closure is carried out directly by reaction with an appropriate acylating agent such as acetic anhydride in a base such as pyridine. The reaction temperature may range from about room temperature to about 130°C, and is preferably about 120°C.

When X is NR^4 wherein R^4 is hydrogen the starting 3-methyl-1H-indazoles can be prepared according to methods described by Behr et al., "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings," Heterocyclic Compounds, R.H. Wiley, Ed., 1967, 289; Bartsch et al., J. Heterocycl. Chem., 1984, 21, 1063; Hannig et al., Pharmazie 1976, 31, 534; Barton et al., J. Chem. Soc. Chem. Comm., 1982, 450; Ruechardt et al., Liebigs Ann. Chem., 1980, 908; and Rees et al., J. Chem. Soc. D, 1971, 827. N-Alkylation of 3-methyl-1H-indazoles (X is NR^4 wherein R^4 is (C_1-C_4)alkyl) can be carried out as described by Behr et al., "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings," Heterocyclic Compounds, R. H. Wiley, Ed., 1967, 309; Palmer et al., J. Chem. Soc., Perkin Trans. II, 1975, 1695; and Claramunt et al., Heterocycles 1985, 23, 2895.

When X is -CH=CH-, the starting 1-methylisoquinolines can be prepared according to the Bischler-Napieralksi or Pictet-Spengler methods (See Organic Reactions, Vol. VI, chapters 2 and 3, pp. 74-190, John Wiley and Sons, New York, 1951).

When X is -N=CH-, the starting 4-methylquinazolines can be prepared according to methods described by Byford et al., Indian J. Chem., 1988, 27B, 396; Higashino, T., Chem. Pharm. Bull., 1962, 10, 1043; and Uff et al., J. Chem. Soc., Perkin Trans. I, 1986, 2295.

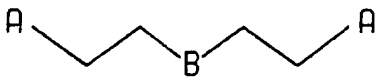
When X is -CH=N- the starting 1-methylphthalazines can be prepared according to methods described by Kant et al., J. Heterocycl. Chem., 1985, 22, 1065 and references cited

therein; Acheson et al., J.Chem. Soc. C, 1966, 2218; and Gabriel et al., Chem. Ber. 1897, 30, 3022.

When X is -N=N-, the starting 4-methyl-1,2,3-benzotriazines can be prepared according to methods described by Adger et al., J. Chem. Soc., Perkin Trans. I, 1975, 31; Boulton et al., Ibid., 1988, 1509; and Rees et al., J. Chem. Soc. D, 1971, 828.

When one or both of R^1 and R^2 are NH_2, the starting material of formula II may be prepared from the corresponding NHAc precursor (Ac=acetyl) by acid hydrolysis. The acid hydrolysis can be carried out with aqueous hydrochoric acid at temperatures ranging from about 50°C to about 120°C. Heating to reflux (about 120°C) in 1N HCl is preferred. The corresponding NHBz (Bz=benzoyl) or $NHSO_2C_6H_5$ compounds can be prepared from the corresponding amino derivative by reaction with the appropriate benzoyl or benzenesulfonyl chloride in the presence of a base such as triethylamine, pyridine, or dimethylaminopyridine. Suitable solvents include methylene chloride, THF, diethylether, or dimethylformamide. Temperatures may range from about -20° to about 80°C. When one or both of R^1 and R^2 is NHBz, it is preferable to use triethylamine/dimethylaminopyridine in methylene chloride at room temperature. When one or both of R^1 and R^2 is $NHSO_2Ph$, it is preferable to use pyridine in methylene chloride at 0°C.

Cyclic dialkylamino compounds of the formula II (i.e., those wherein one or both of R^1 and R^2 are NR^5R^6 wherein NR^5R^6 together form a ring) can also be prepared from the corresponding amino derivative by alkylation with the appropriate bis-halide reagent of the formula

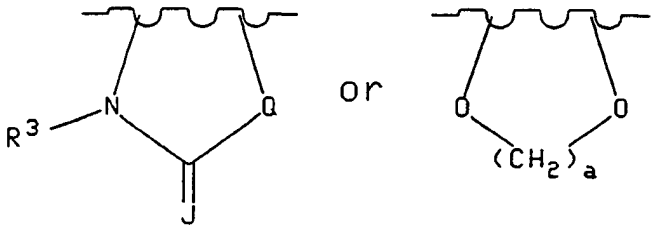


wherein each A is independently bromide or chloride and B is oxygen or $(CH_2)_q$ wherein q is 0 to 2, in the presence of an appropriate base such as triethylamine or diisopropylethylamine (Hunig's base), in an appropriate

nonpolar solvent such as toluene or xylene. The alkylation is typically carried out at a temperature from about room temperature to about 150°C. It is preferably conducted in the presence of Hunig's base in toluene at about 120°C (reflux). (See Verboom et al., J. Org. Chem. 1984, 49, 269).

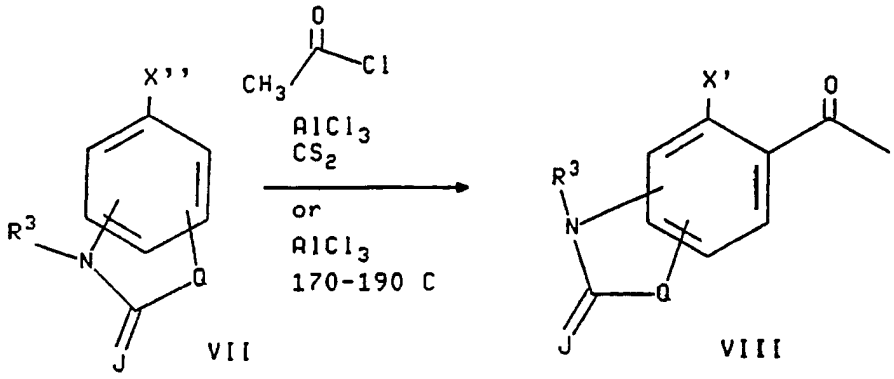
Alternatively, these cyclic dialkylamino derivatives may be prepared by nucleophillic displacement of an aromatic fluoride with the appropriate cyclic amine. Suitable solvents for this reaction include polar aprotic solvents such as dimethylsulfoxide (DMSO), dimethylformamide (DMF), acetonitrile, pyridine and hexamethylphosphoramide. Acetonitrile and pyridine are preferred. The reaction may be run in the presence of a base such as a tertiary or aromatic amines (e.g., triethylamine, diisopropylethylamine, pyridine or dimethylaminopyridine), preferably pyridine or triethylamine. The reaction temperature may range from about room temperature to about 160°C, and is preferably from about 80°C to about 160°C.

When R^1 and R^2, together with the carbons to which they are attached, form a group of the formula



A B

and X is oxygen or sulfur, the starting material of formula II may be prepared by the following procedure which is illustrated only for cases wherein R^1 and R^2 form a group of formula A.



First, a compound of the formula VIII wherein X′ is hydroxy, thiol or methyl sulfide is prepared by Friedel-Crafts acylation of the corresponding compound of the formula VII, wherein X′′ is methoxy or methyl sulfide with an acylating agent such as acetyl chloride or acetic anhydride, preferably acetyl chloride, in the presence of a Lewis acid such as aluminum chloride, titanium tetrachloride or boron triflouride etherate, preferably aluminum chloride. Appropriate solvents include carbon disulfide, 1,2-dichloroethane and nitrobenzene. Carbon disulfide and 1,2-dichloroethane are preferred. Generally, this reaction is conducted at a temperature from about room temperature to about 200°C, preferably from about 50°C to about 100°C.

Alternatively, a compound of formula VIII wherein X′ is hydroxy, may also be obtained by Fries rearrangement of the corresponding compound of the formula VII wherein X′′ is acetyloxy. A mixture of VII and a Lewis acid such as aluminum chloride, boron trifluoride etherate or titanium tetrachloride is heated at temperatures from about 80°C to 200°C either neat or in the presence of a solvent such as nitrobenzene, or 1,2-dichloroethane. The Fries rearrangment is preferably conducted neat with aluminum chloride at 170-190°C.

The compounds of formula VIII obtained by the foregoing process may be converted to the corresponding starting materials of formula II by the procedure described above for 1,2-benzisoxazoles and 1,2-benzisothiazoles.

Referring to scheme 1, compounds of the formula III may be prepared from the corresponding compounds wherein W is hydroxy by methods known in the art. For example, compounds of the formula III wherein W is iodide can be prepared by reacting the hydroxy counterpart with iodine and triphenylphosphine in the presence of a base such as pyridine or imidazole in a non-polar solvent such as benzene or toluene at a temperature from about room temperature to about 130°C. Preferably, the reaction is carried out in benzene in the presence of pyridine at about 90°C (reflux).

Compounds of the formula I-B may be prepared by deprotonating a compound of the formula II with a base in the presence of, or followed by the addition of, an alkylating agent of the formula III wherein R^{10} is phenyl or cinnamyl and W is defined as above. Suitable and preferred bases, solvents and conditions are similar to those described above for the preparation of compounds of the formula IV.

Scheme 2 illustrates the preparation of compounds of the formula I wherein Y is $-CH=CH(CH_2)_n-$ via an aldol-type condensation. These compounds are designated in scheme 2 and hereinafter referred to as compounds of the formula I-C. Referring to scheme 2, a compound of the formula IX wherein R^9 is hydrogen is deprotonated with a base followed by immediate and rapid addition of an aldehyde of the formula X. Suitable bases and solvents are the same as those described above for the first reaction in scheme 1. The reaction temperature may range from about -78°C to about room temperature. The reaction is preferably carried out using lithium diisopropylamide in THF at about -78°C and allowed to warm to room temperature.

If an intermediate alcohol is formed, it can be dehydrated to the olefin under standard acidic conditions, using an acid such as dilute hydrochloric acid, p-toluenesulfonic acid or pyridinium p-toluenesulfonate, preferably p-toluenesulfonic acid, in a solvent such as benzene, toluene, THF or methylene chloride, at a

temperature from about 0°C to about 130°C. Preferably, the dehydration is carried out in benzene at about 80°C (reflux) with azeotropic removal of water. Dehydration may also be accomplished by treatment with Burgess' reagent ($Et_3\overset{+}{N}SO_2N\overset{-}{C}O_2Me$) in methylene chloride or benzene at a temperature from about room temperature to about 80°C.

Alternatively, the intermediate alcohol may be converted into a good leaving group such as mesylate or tosylate and then eliminated with an appropriate base. The mesylate or tosylate can be prepared under standard conditions by reacting the alcohol with methanesulfonyl chloride or p-toluenesulfonyl chloride in the presence of a base such as triethylamine, diisopropylethylamine, or pyridine. Appropriate solvents include methylene chloride and THF, with methylene chloride being preferred. Temperatures may range from about 0°C to about 60°C, and are preferably from about 0°C to about room temperature. Elimination to form the olefin can then be carried out with a base such as diazabicycloundecane or diazabicyclononane in a suitable solvent such as benzene, methylene chloride, or THF, with benzene or methylene chloride being preferred, at a temperature from about 0°C to about 100°C, preferably from about room temperature to about 100°C.

Compounds of the formula I-C may also be prepared by a Wittig reaction from compounds of the formula IX wherein R^9 is bromine, chlorine or iodine. According to this procedure, a compound of formula IX is converted into its phosphonium salt by treatment with triphenylphosphine in a nonpolar solvent such as benzene, toluene or xylene, preferably toluene, at a temperature from about room temperature to about 150°, preferably from about 80°C to about 120°C. The phosphonium salt may then be deprotonated with a strong base such as sodium hydride, potassium t-butoxide, potassium hydride or n-butyllithium in a suitable solvent such as diethylether or THF, at a temperature from about 0°C to about 80°C. The deprotonation is preferably

carried out with sodium hydride in THF at about room temperature.

Scheme 2′ illustrates an alternative preparation of compounds of the formula I wherein X is oxygen or NR^4, Y is $(CH_2)_m$ or $-CH=CH(CH_2)_n$ and M is carbon (i.e. -CH-). These compounds are designated in Scheme 2′, and hereinafter referred to as compounds of the formula I-F (those where Y is $-CH=CH(CH_2)_{n'}$ and n′ is an integer from 0 to 3) and I-G (those where Y is $(CH_2)_m$ and n′ is an integer from 0 to 1). Referring to Scheme 2′, compounds of the formula I-F may be prepared by deprotonating a compound of the formula XV with a suitable base followed by addition of an aldehyde of formula XVI to give an intermediate of formula XVII. This intermediate is then transformed to compounds of the formula I-F by reaction with an appropriate amine.

Appropriate bases for use in the preparation of compounds of the formula XVII include lithium diisopropylamide, lithium or sodium or potassium hexamethyldisilazide, or n-butyllithium, preferably lithium diisopropylamide or lithium hexamethydisilazide. The reaction of a compound of formula XV with a compound of formula XVI is generally carried out in a polar aprotic solvent such as diethyl ether, 1,2-dimethoxyethane, or tetrahydrofuran. Temperatures may range from -78°C to 80°C. This reaction is preferably conducted in THF at -78°C and allowed to warm to room temperature.

A compound of formula I-F is then obtained from an intermediate of formula XVII by reaction with an amine such as hydrazine or hydroxylamine in the presence of a base such as sodium or potassium hydroxide, sodium or potassium carbonate, or sodium or potassium alkoxide (methoxide or ethoxide), preferably sodium or potassium hydroxide. In some cases (when amine is hydrazine), addition of a base may not be necessary. Suitable solvents for this reaction include methanol, ethanol, i-propanol, water, or, when amine is hydrazine, hydrazine itself may be used as a solvent. Temperatures may range from 50°C to 120°C. It is preferable

to react XVII with hydrazine at 120°C (reflux), or with hydroxylamine and potassium hydroxide in EtOH/water at 100°C (reflux). Upon reaction with hydroxylamine, the intermediate oxime obtained may be isolated and then cylclized to compounds of the formula I-F following the suitable and preferred conditions described above for the preparation of starting materials 3-methyl-1,2-benzioxazoles.

Compounds of the formula I-G may be prepared by reducing an intermediate of formula XVII to give a compound of formula XVIII. The intermediate of formula XVII may then be reacted with an amine to give compounds of the formula I-G. An intermediate of formula XVII is reduced with hydrogen gas to an intermediate of formula XVIII in the presence of a catalyst such as palladium on carbon, platinum oxide, or rhodium on carbon, preferably platinum oxide in a polar solvents such as ethyl acetate, tetrahydrofuran, ethanol, or acetic acid, preferably EtOH. Pressure may range from atmospheric to 50 psi, preferably 40-50 psi and temperature may range from room temperature to 80°C, preferably room temperature.

A compound of formula I-G is then obtained from an intermediate of formula XVIII following the suitable and preferred conditions described above for the preparation a compound of formula I-F from an intermediate of formula XVII.

Scheme 3 illustrates the preparation of compounds of the formula I wherein Y is $-O(CH_2)_m-$ or $-NR^4(CH_2)_m$. These compounds are designated in scheme 3 and hereinafter referred to as compounds of the formula I-D. Referring to scheme 3, compounds of the formula I-D may be prepared by reacting a compound of the formula XI wherein R^{12} is chloro or bromo, with a nucleophile of the formula XII, wherein Z is $-NHR^4$ or -OH. When Y is $NR^4(CH_2)_m$ (i.e., Z is $-NHR^4$), the amine of formula XII is generally reacted with the appropriate compound of formula XI either neat or in a polar solvent such as dimethylformamide (DMF), dimethylsulfoxide

(DMSO), THF or pyridine. DMSO and DMF are preferred solvents. An acid acceptor such as diazabicycloundecane, pyridine, lutidine, triethylamine or metal carbonates such as potassium or sodium or cesium carbonate may be added. Metal carbonates such as potassium carbonate are preferred. The reaction temperature may range from about room temperature to about 160°C and is preferably from about 100°C to about 160°C.

When Y is $O(CH_2)_m$ (i.e., Z is -OH), the alkoxide anion is formed and this species is reacted with the compound of formula XI. According to this procedure, the alcohol (XII) is deprotonated with a suitable base, after which the appropriate compound of formula XI is added and the mixture is heated. Examples of suitable bases are sodium, sodium hydride and potassium hydride with sodium hydride being preferred. Suitable solvents include THF, DMF and DMSO, with THF and DMF being preferred. This reaction is generally conducted at a temperature from about 40°C to about 160°C. Temperatures between about 60°C and about 160°C are preferred.

Alternatively, compounds of the formula I-D may be prepared by reacting a compound of formula XI with a nucleophile of the formula XIX wherein Z and R^{10} are defined as above. This reaction produces an intermediate of formula XX which is then deprotected to yield a secondary piperidine of formula XXI as a free base or a salt of the free base, after which such free base or salt is alkylated with a compound of the formula WL, wherein W is defined as above and L is phenyl(C_1-C_6)alkyl, pyridylmethyl, or a group of the formula K.

Suitable and preferred bases, solvents, and conditions for the reaction of a compound of formula XI with a nucleophile of the formula XIX are similar to those described for the reaction of a compound of the formula XI with a nucleophile of the formula XII for the preparation of compounds of the formula I-D. Suitable and preferred bases, solvents, and conditions for the transformations of

compounds of the formulas XX and XXI to prepare compounds of the formula I-D are similar to those described in scheme 1 for compounds of the formulas IV and VI to prepare compounds of the formula I-A.

Scheme 4 illustrates the preparation of compounds of the formula I wherein Y is $-(CH_2)_m-$ and M is nitrogen. These compounds are designated in scheme 4 and hereinafter referred to as compounds of the formula I-E. Referring to scheme 4, a compound of the formula XIII wherein R^{12} is chloro, bromo or iodo is reacted with a compound of the formula XIV. This reaction may be carried out in the presence of an acid acceptor such as pyridine, 2,6-lutidine or a metal carbonate (e.g., sodium bicarbonate or sodium or potassium carbonate). When R^{12} is chloro or bromo, a catalytic amount of a displacement promoter may be added. Examples of suitable displacement promoters are sodium iodide, potassium iodide or tetra-n-butylammonium iodide. Generally, this reaction is conducted in a nonpolar solvent such as toluene or xylene, or in a polar solvent such as THF, DMF or DMSO, preferably xylene or DMF, at a temperature from about room temperature to about 160°C, preferably from about 90°C to about 160°C.

Scheme 5 illustrates the preparation of compounds of the formula I wherein X is -N=CH- and M is carbon (i.e. -CH). These compounds are designated in scheme 5 and hereinafter referred to as compounds of the formula I-H. Referring to scheme 5, a compound of the formula II' may be deprotonated with one equivalent of a base followed by addition of a silylating agent (trimethylsilyl chloride). Sequential deprotonation with a second equivalent of the same base followed by addition of an alkylating agent of the formula III and appropriate work-up produces an intermediate of the formula IV'. This intermediate is then deprotected as described in scheme I to yield a secondary piperidine of formula VI' as a free base or a salt of the free base, after which such free base or salt is alkylated with a compound of the formula WL, wherein W is defined as above and L is

phenyl(C_1-C_6)alkyl, pyridylmethyl, or a group of the formula K.

Suitable bases, solvents, and temperatures for deprotonation of a compound of the formula II' are the same as those described above for the first reaction in scheme I, preferably LDA in THF at 0° to room temperature. After addition of the first equivalent of base, a silylating agent such as trimethylsilyl or triethylsilyl chloride is added, preferably trimethylsilyl chloride. A second equivalent of the same base is then added followed by an alkylating agent of the formula III. The trimethylsilyl group is then removed under acidic conditions by stirring the crude reaction mixture with dilute hydrochloric acid for 30-60 min at room temperature. Then, the crude reaction mixture is made basic with aqueous sodium carbonate, or aqueous sodium or potasium hydroxide, preferably aqueous sodium hydroxide, and the intermediate of formula IV'is extracted with an organic solvent by conventional extraction techniques. Suitable and preferred conditions for the transformation of intermediates of the formula IV' to compounds of the formula I-H are the same described in scheme I for the preparation of compounds of the formula I-A.

Scheme 6 illustrates the preparation of compounds of the formula I wherein Y is $(CH_2)_m$. M is carbon (i.e. -CH-), J is sulfur and Q is $CHCH_3$, $C(CH_3)_2$, -CH=CH, or $(CH_2)_1$. These compounds are designated in scheme 6 and hereinafter referred to as compounds of the formula I-I. Referring to scheme 6, a compound of the formula I-I may be prepared from the corresponding compound of the formula IV" where J is oxygen by reacting with a phosphorus sulfide to give an intermediate of the formula XXII. This intermediate is then deprotected as described in scheme I to yield a secondary piperidine of formula VI" as a free base or a salt of the free base, after which such free base or salt is alkylated with a compound of the formula WL, wherein W is defined as above and L is phenyl(C_1-C_6)alkyl, pyridylmethy, or a group of the formula K.

The transformation of a compound of formula IV" to an intermediate of formula XXII is carried out with a phosphorous sulfide such as phosphorous pentasulfide (P_2S_{10}) or Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] in an non-polar solvent such as benzene, toluene, or xylene. Temperatures may range from 50°C to 160°C. Lawesson's reagent in toluene at 80°C is preferred. Suitable and preferred conditions for the transformation of intermediates of the formula XXII to compounds of the formula I-I are the same ones described in scheme 1 for the preparation of compounds of the formula I-A.

Scheme 7 illustrates the preparation of compounds of the formula I wherein Y is $(CH_2)m$, M is carbon (i.e. -CH-), and R^3 is (C_1-C_6) alkyl. These compounds are designated in scheme 7 and hereinafter referred to as compounds of the formula I-J. Referring to scheme 7, a compound of the formula I-J may be prepared from the corresponding compounds of the formula IV''' where R^3 is hydrogen by deprotonating with a base followed by addition of the appropriate alkylating agent (preferably the appropriate (C_1-C_6) alkyl chloride, bromide, or iodide) to give an intermediate of formula XXIII. This intermediate is then deprotected as described in scheme 1 to yield a secondary piperidine of formula VI''' as a free base or a salt of the free base, after which such base or salt is alkylated with a compound of the formula WL, wherein W is defined as above and L is phenyl(C_1-C_6)alkyl, pyridylmethyl, or a group of the formula K.

Suitable bases for the transformation of a compound of the formula IV''' to a compound of the formula XXIII include sodium hydride, potassium hydride, lithium diisopropylamide, or n-butyllithium, preferably sodium hydride. The reaction is generally carried out in a polar aprotic solvent such as tetrahydrofuran, dimethylformamide, or 1,2-dimethoxyethane and temperatures may range from -78°C to 80°C. The reaction is preferably conducted in dimethylformamide at room

temperature. Suitable and preferred conditions for the transformation of intermediates of the formula XXIII to compounds of the formula I-J are the same described in scheme 1 for the preparation of compounds of the formula I-A.

Alternatively, a compound of the formula I-J may be prepared directly from the corresponding compound of the formula I-A′ wherein L is phenyl-(C_1-C_6) alkyl, pyridylmethyl or a group of the formula K and R^3 is hydrogen or I-B′ wherein L is phenyl or cinnamyl and R^3 is hydrogen. Compounds of the formula I-A′ and I-B′ are prepared according to the methods described in scheme 1 for the preparation of compounds I-A and I-B. Suitable and preferred bases, solvents, and conditions for the transformation of compounds of the formula I-A′ and I-B′ to compounds of the formula I-J are the same described above for the preparation of compounds of the formula XXIII.

When one or both of R^1 and R^2 are OH, compounds of the formula I may be prepared from the corresponding -OMe precursor by dealkylation with a Lewis acid such as aluminum trichloride, boron trichloride, boron tribromide, or a protic acid such as aqueous hydrochloric or hydrobromic acid. Suitable solvents for the reaction with Lewis acids include non-polar solvents such as benzene, toluene, dichloromethane, or 1, 2-dichlorethane. Temperatures may range from -78°C to 120°C. Aqueous hydrobromic acid (48%) at 100-120°C (reflux) is preferred.

When one or both of R^1 and R^2 are NH_2, compounds of the formula I may be prepared from the corresponding NHAc precursor (Ac=acetyl) by acid hydrolysis under the suitable and preferred conditions described above for the formation of starting materials of formula II wherein one or both of R^1 and R^2 are NH_2. The corresponding nitrile (-CN) compounds can be prepared from the corresponding amino compounds via a diazonium salt formation by reacting the amino compound with nitrous acid (made from aqueous hydrochloric acid and sodium nitrite) followed by neutralization and addition to

CuCN. Suitable solvents include polar protic solvents such as water or biphasic mixtures with non-polar solvents such as benzene, toluene, or xylene. Neutralization may be carried out by adding a base such as sodium carbonate, potassium carbonate, sodium hydroxide, or potassium hydroxide until pH 7. Temperatures may range from -20°C to 60°C. It is preferable to carry out the diazonium salt formation in water at 0°C, to neutralize with sodium carbonate, and to add the diazonium salt to a biphasic mixture of aqueous CuCN and toluene at 0°C, followed by heating to 50°C.

When one or both of R^1 and R^2 are carboxamide ($-CONH_2$), compounds of the formula I may be prepared from the corresponding nitrile (-CN) precursor by reaction with a base such as sodium hydroxide, potassium hydroxide or tetramethylammonium hydroxide in a polar solvent such as water, methanol, ethanol, or t-butanol. Temperatures may range from room temperature to 120°C. Potassium hydroxide in t-butanol at 85-100°C is preferred.

Compounds of the formula I other than those of formulae I-A-I-J may be prepared by methods that will be obvious to those skilled in the art from the procedures described above and other known methods.

In each of the above reactions, pressure is not critical. Pressures in the range of about 0.5 atm to 3 atm are suitable, and ambient pressure (generally, about one atmosphere) is preferred as a matter of convenience. Also, for those reactions where the preferred temperature varies with the particular compounds reacted, no preferred temperature is stated. For such reactions, preferred temperatures for particular reactants may be determined by monitoring the reaction using thin layer chromatography.

The compounds of formula I and their pharmaceutically acceptable salts (hereinafter referred to as the "active compounds of the invention") may be administered to a patient by various methods, for example, orally as capsules or tablets, parentally as a sterile solution or suspension,

and in some cases intravenously in the form of a solution. The free base compounds of the invention may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts.

The daily dose of the active compounds of the invention is generally in the range of from about 1 to 300 mg/day for the average adult human, and may be administered in single or divided doses.

When incorporated for parenteral administration into a solution or suspension, the active compounds of the invention are present in a concentration of at least 1 weight percent, and preferably between about 4 to 70 weight percent (based on the total weight of the unit). The parenteral dosage unit typically contains between about 5 to 100 mg of active compound(s).

The active compounds of the invention may be administered orally with an inert diluent or an edible carrier, or they may be enclosed in gelatin capsules or compressed into tablets. Such preparations should contain at least 0.5% of active compound(s), but the concentration may vary depending upon the particular form and may be from 4 to 70 weight percent (based on the total weight of the unit). The oral dosage unit typically contains between 1.0 mg to 300 mg of active compound.

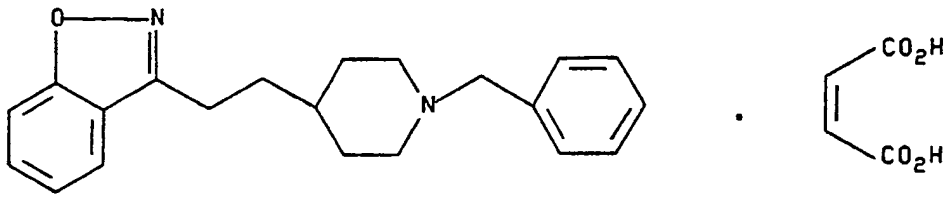
The cholinesterase inhibiting activity of the active compounds of the invention may be determined by a number of standard biological or pharmacological tests. One such procedure for determining cholinesterase inhibition is described by Ellman et al. in "A New and Rapid Colorimetric Determination of Acetylcholinesterase Activity", Biochem. Pharm. 1, 88, (1961).

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) and C^{13} nuclear magnetic resonance spectra (C^{13} NMR) were measured for solutions in

deuterochloroform ($CDCl_3$) except where otherwise noted and peak positions are expressed in parts per million (ppm). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Frequencies (J) are expressed in Hertz. 1 M solutions of lithium diisopropylamide were freshly prepared by adding n-butyllithium (1.6-2.5 M in hexanes) to a solution of diisoproylamine in tetrahydrofuran at 0°.

Example 1

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate



a) 1,4-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl)ester, 4-ethyl ester.

A solution of ethyl isonipecotate (20.0 g,0.127 mol) and triethylamine (17.8 mL, 0.127 mol) in 1:1 dioxane-H_2O (1.2 L) was cooled to 0°C. After 15 min, t-BOC-anhydride (35.2 g, 0.161 mol) was added and the resulting mixture was allowed to warm to room temperature overnight. The mixture was extracted with ethyl acetate (4 times) and the combined organic layer was washed with 1N hydrochloric acid, water and brine, and then dried (magnesium sulfate), filtered, and concentrated to give a light orange oil. A Kugelrhor distillation (0.05 torr, 80-90°C) gave the title carbamate (30.69 g, 94%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 4.11 (q, 2H, J=7.2Hz), 3.97-4.05 (m, 2H), 2,80 (br t, 2H, J-11.6Hz), 2.40 (tt, 1H, J=11.0Hz, J=3.9Hz), 1.81-1.86 (m, 2H), 1.52-1.66 (m, 2H), 1.43 (s, 9H), 1.23 (t, 3H, J=7.2Hz).

b) 4-Hydroxymethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester.

Lithium aluminum hydride (4.3 g,0.114 mol) was added to a cold solution (0°C) of the carbamate formed in step a (26.57 g, 0.103 mol) in tetrahydrofuran (THF) (1L). After 30 min, the ice bath was removed and the reaction mixture was allowed to stir overnight at room temperature. Sodium sulfate decahydrate was added carefully until the evolution of gas subsided. After stirring for 1 hour, the mixture was filtered through a Celite pad and the filtrate was concentrated. Recrystallization (ethyl ether/hexanes) gave the title alcohol (20.67 g, 93%) as a white solid.

^{1}H-NMR ($CDCl_3$) δ 4.04-4.26 (m, 2H), 3.49 (d, 2H, J=6.4 Hz), 2.70 (brt, 2H, J=12.0Hz), 1.6-1.73 (m, 3H), 1.47 (s, 9H), 1.15 (ddd, 2H, J=23.2Hz, J=12.0Hz, J=4.3Hz).

c) 4-Iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester.

Triphenylphosphine (31.0 g, 0.119 mol) was added to a mixture of iodine (29.0 g,0.114 mol) in benzene (1L). After 5 min, pyridine (18.5 ml, 0.228 mol) followed by the alcohol formed in step b (20.5 g, 0.095 mol) was added. The resulting mixture was heated to reflux for 1.5 hours. The cooled reaction mixture was filtered, and the filtrate was washed with saturated sodium thiosulfate ($Na_2S_2O_3$) and brine, and dried (magnesium sulfate), filtered, and concentrated. Purification by silica gel chromatography (10% → 20% ethyl acetate/hexanes) gave the title iodide (28.5 g, 92%) as a clear oil. Upon cooling, a white solid was obtained.

M.p.: 58-59°C.

^{1}H-NMR ($CDCl_3$) δ 4.09 (br d, 2H, J=13.1Hz), 3.08 (d, 2H, J=6.5Hz), 2.66 (br t, 2H, J=13.1Hz), 1.80 (br d, 2H, J=12.9Hz), 1.52-1.64 (m, 1H), 1.43 (s, 9H), 1.11 (ddd, 2H, J=24.7Hz, J=12.7Hz, J=4.3Hz).

d) 4-[2-[1,2-Benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester.

A mixture of 3-methyl-1,2-benzisoxazole (0.410 g, 3.08 mmol) and the iodide formed in step c (1.05 g, 3.23 mmol) in

dry THF (3.2 mL) was cooled to -78°C. Freshly prepared 1M lithium diisopropylamide (LDA) (3.1 mL, 3.1 mmol) was added dropwise and the resulting yellow-orange solution was stirred for 25 min at -78°C. Saturated ammonium chloride was added and the mixture was extracted with ethyl acetate (3 times). The combined organic layer was washed with brine and then dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (10% → 20% ethyl acetate/hexanes) gave the title compound (0.430 g, 42%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 7.62 (d, 1H, J=8.0Hz), 7.49-7.55 (m, 2H), 7.25-7.31 (m, 1H), 4.09 (m, 2H), 3.00 (t, 2H, J=7.8Hz), 2.66 (br t, 2H, J=13.0Hz), 1.71-1.84 (m, 4H), 1.47-1.53 (m, 1H), 1.43 (s, 9H), 1.14 (ddd, 2H, J=24.5Hz, J-12.1Hz, J=4.1Hz).

e) 3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate.

Trifluoroacetic acid (TFA) (7 mL) was added dropwise to a cold (0°C) solution of the piperidine formed in step d (0.50 g, 1.51 mmol) in methylene chloride (7 mL). The resulting solution was stirred at 0°C for 30 min. Volatiles were removed under reduced pressure and excess TFA was removed by concentrating from toluene twice. The crude product was redissolved in methylene chloride (10 mL) and then triethylamine (0.42 mL, 3.01 mmol) and benzyl bromide (0.18 mL, 1.51 mmol) were added. The resulting mixture was stirred overnight (15 hours) at room temperature. The mixture was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (50% ethyl acetate/hexanes) gave the title compound (free base) (0.350 g, 73%) as a colorless oil.

The maleate salt was prepared by adding a solution of maleic acid (0.108 g, 0.930 mmol) in ethyl ether (20 mL) to a solution of the free base (0.297 g, 0.926 mmol) in ethyl ether (20 mL). The white solid formed was collected and rinsed with ethyl ether. Yield: 0.35 g, 87%.

M.p. 146.4-147.6°C.

EIMS (no parent) 319.1, 303.1, 185.2, 172.1, 91.1

^{1}H NMR ($CDCl_3$) δ 7.60 (d, J=8, 1H), 7.51-7.52 (m, 2H), 7.37-7.49 (m, 5H), 7.25-7.32 (m, 1H), 6.30 (s, 2H), 4.16 (s, 2H), 3.45-3.51 (m, 2H), 2.98 (t, J=7.4, 2H), 2.60-2.70 (m, 2H), 1.84-1.95 (m, 4H), 1.60-1.82 (m, 3H).

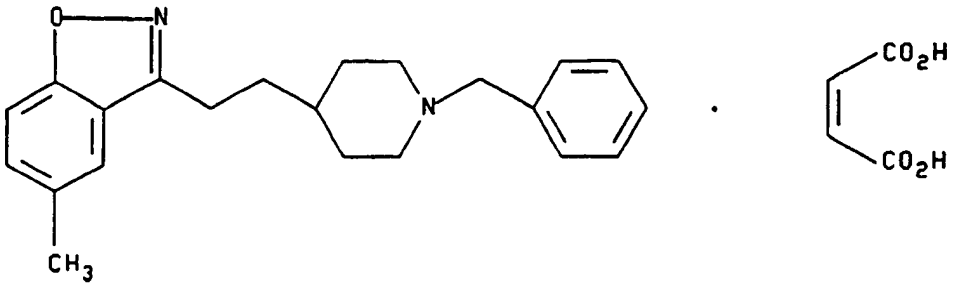
^{13}C NMR δ 169.5, 163.0, 157.7, 135.8, 131.1, 130.1, 130.0, 129.3, 128.5, 123.5, 121.3, 121.1, 110.0, 60.6, 52.1, 32.8, 28.8, 22.1.

IR (KBr) 2944, 2927, 2921, 2499-2518 (broad), 2329-2388 (broad), 1583, 1517, 1473, 1458, 1445, 1438, 1383, 1360, 782 cm^{-1}.

Calc'd for $C_{21}H_{24}N_2O \bullet C_4H_4O_4$:C, 68.79; H, 6.47; N, 6.42. Found: C, 68.80; H, 6.35; N, 6.27.

Example 2

5-Methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate



a) 4-[2-[5-Methyl-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester

The procedure described in Example 1d was followed using 3,5-dimethyl-1,2-benzisoxazole (0.500 g, 3.40 mmol), 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (1.20 g, 3.74 mmol), and 1M lithium diisopropylamide (LDA) (3.74 mL, 3.74 mmol) in dry THF (5 mL). After purification, the title compound (0.910 g, 78%) was obtained as a clear oil.

^{1}H-NMR ($CDCl_3$) δ 7.28-7.40 (m, 3H), 4.04-4.11 (m, 2H), 2.94 (t, 2H, J=7.8Hz), 2.64 (br t, 2H, J=12.3Hz), 2.43 (s,

3H), 1.70-1.99 (m, 4H), 1.42 (s, 9H), 1.41-1.55 (m, 1H), 1.13 (ddd, 2H, J=24.4Hz, J=12.0Hz, J=4.1Hz).

b) 5-Methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate

The procedure described in Example 1e was followed using the piperidine formed in step a (0.910 g, 2.64 mmol) and TFA (13 mL) in methylene chloride (CH_2Cl_2) (13 mL), and triethylamine (3.7 mL, 26.4 mmol) and benzyl bromide (0.32 mL, 2.69 mmol) in methylene chloride (CH_2Cl_2) (20 mL). After purification, the title compound (free base) (0.56 g, 63%) was obtained as a clear oil.

The maleate salt was prepared by adding a solution of maleic acid (0.20 g, 1.72 mmol) in ethyl ether (Et_2O) (10 mL) to a solution of the free base (0.56 g, 1.67 mmol) in Et_2O (40 mL). The white solid formed was collected and rinsed with Et_2O. Yield: 0.70 g, 93%.

M.p. 149-151°C.

^1H NMR ($CDCl_3$) δ 7.27-7.43 (m, 8H), 6.32 (s, 2H), 4.17 (s, 2H), 3.51 (br d, J=11.6, 2H), 2.96 (t, J=7.3, 2H), 2.66 (br t, J=10.8, 2H), 2.45 (s, 3H), 1.60-1.97 (m, 7H).

^{13}C NMR δ 169.4, 161.6, 157.3, 135.7, 133.2, 131.6, 131.0, 130.1, 129.3, 128.4, 121.4, 120.2, 60.6, 52.0, 32.8, 32.7, 28.7, 22.0, 21.1.

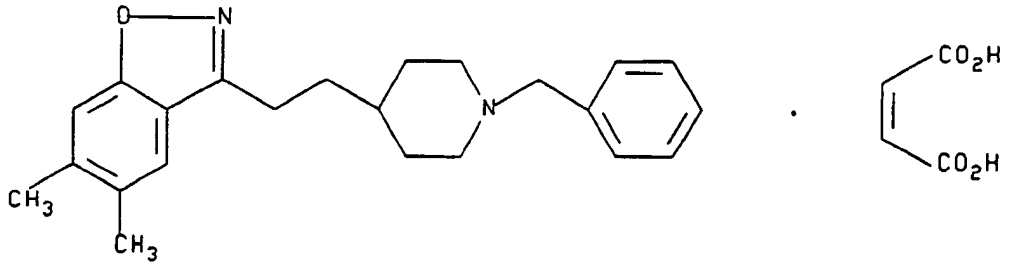
IR (KBr) 2934, 2848, 2499, 2362, 1701, 1617, 1572, 1487, 1454, 1357 cm^{-1}.

EIMS (no parent) 333.1, 317.2, 185.1, 172.1, 91.1 (base).

Calc'd for $C_{22}H_{26}N_2O \bullet C_4H_4O_4$: C, 69.32; H, 6.71; N, 6.22. Found: C, 69.18; H, 6.48; N, 6.08.

Example 3

5,6-Dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate



a) 4-[2-[5,6-Dimethyl-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester

The procedure described in Example 1d was followed using 3,5,6-trimethyl-1,2-benzisoxazole (0.600 g, 3.73 mmol), 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester (1.30 g, 4.10 mmol), and 1M LDA (4.10 mL, 4.10 mmol) in dry THF (10 mL). After purification, the title compound (1.04 g, 78%) was obtained as a clear oil.

^{1}H-NMR ($CDCl_3$) δ 7.32 (s, 1H), 7.27 (s, 1H), 4.04-4.10 (m, 2H), 2.93 (t, 2H, J=7.8Hz), 2.64 (br t, 2H, J=11.9Hz), 2.35 (s, 3H), 2.32 (s, 3H), 1.70-1.80 (m, 4H), 1.43 (s, 9H), 1.43-1.51 (m, 1H), 1.13 (ddd, 2H, J=24.3Hz, J=12.3Hz, J=4.2Hz).

b) 5,6-Dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate

The procedure described in Example 1e was followed using the piperidine formed in step a (1.04 g, 2.90 mmol) and TFA (16 mL) in CH_2Cl_2 (16 mL), and triethylamine (4.2 mL, 29.0 mmol) and benzyl bromide (0.36 mL, 3.03 mmol) in CH_2Cl_2 (20 mL). After purification, the title compound (free base) (0.53 g, 52%) was obtained as a clear oil.

The maleate salt was prepared by adding a solution of maleic acid (0.18 g, 1.55 mmol) in Et_2O (10 mL) to a solution of the free base (0.53 g, 1.52 mmol) in Et_2O (25 mL). The white solid formed was collected and rinsed with Et_2O. Yield: 0.65 g, 92%.

M.p. 182-183.5 °C.

^{1}H NMR ($CDCl_3$) δ 7.30-7.41 (m, 7H), 6.32 (s, 2H), 4.17 (s, 2H), 3.51 (br d, J=11.8, 2H) 2.95 (t, J=7.2, 2H) 2.65 (br t, J=11.7, 2H), 2.38 (s, 3H), 2.34 (s, 3H), 1.59-1.96 (m, 7H).

^{13}C NMR δ 169.4, 162.3, 157.1, 140.2, 135.7, 132.6, 131.1, 130.1, 129.3, 128.3, 120.3, 119.2, 110.0, 60.6, 52.0, 32.7, 28.7, 22.0, 20.9, 19.9.

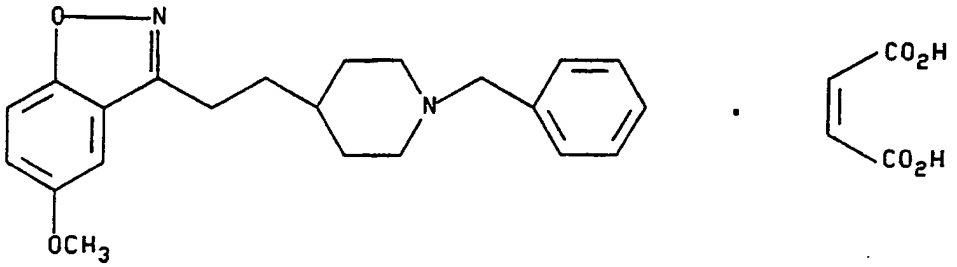
EIMS 347.2, 331.1, 185.1, 172.1, 91.1, (base)

IR (KBr) 2949, 2914, 2512, 2420, 1580, 1476, 1456, 1449, 1358 cm^{-1}.

Calc'd for $C_{23}H_{28}N_2O \cdot C_4H_4O_4 \cdot 1/4H_2O$:C, 69.14; H, 6.93; N, 5.97. Found: C, 69.27; H, 6.83; N, 5.91.

Example 4

5-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate



a) 4-[2-[5-Methoxy-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester

The procedure described in Example 1d was followed using 5-methoxy-3-methyl-1,2-benzisoxazole (0.32 g, 1.96 mmol), 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester (0.70 g, 2.15 mmol), and 1M LDA (2.0 mL, 2.0 mmol) in dry THF (2 mL). After purification, the title compound (0.62 g, 87%) was obtained as a clear oil.

^{1}H-NMR ($CDCl_3$) δ 7.46 (d, 1H, J=9.1Hz), 7.17 (dd, 1H, J=9.1Hz, J=2.5Hz), 6.96 (d, 1H, J=2.4Hz), 4.09-4.16 (m, 2H), 3.87 (s, 3H), 2.99 (t, 2H, J=7.8 Hz), 2.69 (br t, 2H, J=12.3Hz), 1.74-1.85 (m, 4H), 1.46-1.64 (m, 1H), 1.46 (s, 9H), 1.17 (ddd, 2H, J=22.3 Hz, J=12.2Hz, J=4.2Hz).

b) 5-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate

The procedure described in Example 1e was followed using the piperidine formed in step a (0.58 g, 1.61 mmol) and TFA (7 mL) in CH_2Cl_2 (7 mL), and triethylamine (0.50 mL, 3.6 mmol) and benzyl bromide (0.195 mL, 1.64 mmol) in CH_2Cl_2 (10 mL). After purification, the title compound, free base (0.27 g, 48%) was obtained as a clear oil.

The maleate salt was prepared by adding a solution of maleic acid (0.080 g, 0.69 mmol) in Et_2O (10 mL) to a solution of the free base (0.24 g, 0.68 mmol) in Et_2O (20 mL). The white solid formed was collected and rinsed with Et_2O. Yield: 0.29 g, 91%.

M.p. 143.5-145°C

^1H NMR ($CDCl_3$) δ 7.35-7.42 (m, 6H), 7.13 (dd, J_1=9.1, J_2=2.5, 1H), 6.92 (d, J=2.4, 1H), 6.30 (s, 2H), 4.17 (s, 2H), 3.83 (s, 3H), 3.46-3.51 (m, 2H), 2.94 (t, J=7.3, 2H), 2.60-2.80 (m, 2H), 1.60-1.96 (m, 7H).

^{13}C NMR δ 169.4, 158.4, 157.6, 156.3, 135.8, 131.0, 130.0, 129.2, 128.4, 121.5, 120.3, 110.6, 101.1, 60.5, 56.0, 52.0, 32.7, 32.5, 28.7, 22.0.

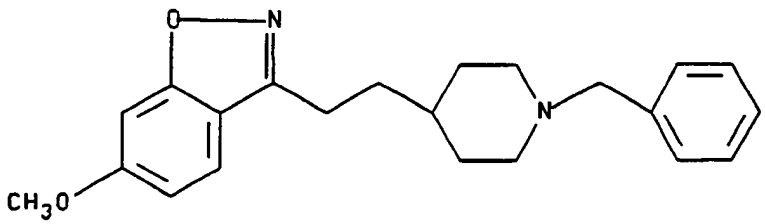
IR (KBr) 2942, 2927, 2916, 2518, 2366, 1616, 1572, 1544, 1521, 1480, 1454, 1443, 1384, 1357, 1220 cm^{-1}.

EIMS 349.2, 333.2, 318.1, 259.1, 185.1, 172.1, 91.1 (base).

Calc'd for $C_{22}H_{26}N_2O_2 \bullet C_4H_4O_4$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.21; H, 6.52; N, 5.94.

Example 5

6-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole



a) 4-[2-[6-Methoxy-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester

The procedure described in Example 1d was followed using 6-methoxy-3-methyl-1,2-benzisoxazole (0.32 g, 1.96 mmol), 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester (0.70 g, 2.15 mmol), and 1M LDA (2.0 mL, 2.0 mmol) in dry THF (3 mL). After purification, the title compound (0.57 g, 80%) was obtained as a white solid.

M.p.: 95-96°C

^{1}H-NMR ($CDCl_3$) δ 7.47 (d, 1H, J=8.7Hz), 6.99 (d, 1H, J=2.1Hz) 6.91 (dd, 1H, J=8.6Hz, J=2.1Hz), 4.08-4.11 (m, 2H), 3.89 (s, 3H), 2.97 (t, 2H, J=7.8 Hz), 2.68 (br t, 2H, J=12.7Hz), 1.72-1.84 (m, 4H), 1.46-1.60 (m, 1H), 1.46 (s, 9H), 1.16 (ddd, 2H, J=24.6 Hz, J=12.3Hz, J=4.3Hz).

b) 6-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole

The procedure described in Example 1e was followed using the piperidine formed in step a (0.49 g, 1.36 mmol) and TFA (7 mL) in CH_2Cl_2 (7 mL), and triethylamine (0.85 mL, 6.1 mmol) and benzyl bromide (0.165 mL, 1.39 mmol) in CH_2Cl_2 (8 mL). After purification, the title compound (0.265 g, 55%) was obtained as a white solid.

M.p. 90.5-91.5°C.

^{1}H NMR ($CDCl_3$) δ 7.47 (d, J=8.7, 1H), 7.21-7.33 (m, 5H), 6.98 (d, J=1.8, 1H), 6.90 (dd, J_1=8.7, J_2=2.0, 1H), 3.88 (s, 3H), 3.50 (s, 2H), 2.88-2.98 (m, 4H), 1.96 (br t, J=10.6, 2H), 1.74-1.83 (m, 4H), 1.27-1.34 (m, 3H).

^{13}C NMR δ 164.8, 162.0, 158.3, 138.4, 129.2, 128.1, 126.9, 121.4, 115.0, 113.8, 92.6, 63.4, 55.7, 53.7, 35.3, 34.3, 32.6, 22.6.

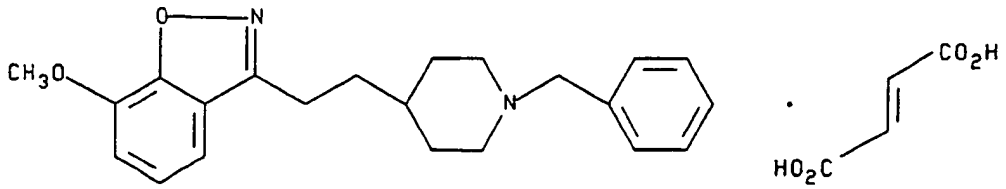
IR (KBr) 2924, 2913, 2797, 2758, 1625, 1608, 1276, 1196, 1154, 734 cm^{-1}.

EIMS 349.2, 333.6, 259.1, 185.1, 172.1, 91.0 (base).

Calc'd for $C_{22}H_{26}N_2O_2$:C, 75.40; H, 7.48; N, 7.99. Found: C, 75.52; H, 7.63; N, 7.94.

Example 6

7-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole fumarate



a) 4-[2-[7-Methoxy-1,2-benzisoxazol-3-yl]ethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester

The procedure described in Example 1d was followed using 7-methoxy-3-methyl-1,2-benzisoxazole (0.30 g, 1.84 mmol), 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester (0.60 g, 1.85 mmol), and 1M LDA (1.9 mL, 1.9 mmol) in dry THF (2 mL). After purification, the title compound (0.41 g, 62%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 7.12-7.19 (m, 2H), 6.91 (dd, 1H, J=6.5Hz, J=2.2Hz), 3.98-4.07 (m, 2H), 3.98 (s, 3H), 2.95 (t, 2H, J=7.8 Hz), 2.62 (br t, 2H, J=12.2Hz), 1.67-1.78 (m, 4H), 1.40-1.48 (m, 1H), 1.40 (s, 9H), 1.10 (ddd, 2H, J=24.5 Hz, J=12.5Hz, J=4.3Hz).

b) 7-Methoxy-3-[-2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole fumarate

The procedure described in Example 1e was followed using the piperidine formed in step a (0.40 g, 1.11 mmol) and TFA (6 mL) in CH_2Cl_2 (6 mL), and triethylamine (0.34 mL, 2.44 mmol) and benzyl bromide (0.14 mL, 1.18 mmol) in CH_2Cl_2 (10 mL). After purification, the title compound (free base) (0.080 g, 21%) was obtained as a clear oil.

The fumarate salt was prepared by adding a solution of fumaric acid (0.025 g, 0.213 mmol) in ethanol (EtOH) (2 mL) to a solution of the free base (0.071 g, 0.203 mmol) in Et_2O (10 mL). Upon concentration to 4-5 mL, a white/pink solid precipitated. This solid was collected and rinsed with Et_2O. Yield: 0.065 g, 69%.

M.p. 138-139°C.

^{1}H NMR ($CDCl_3$) δ 7.27-7.41 (m, 7H), 7.19 (d, J=7.7, 1H), 6.59 (s, 2H), 3.97 (s, 3H), 3.65 (s, 2H), 2.90-3.01 (m, 4H), 2.18 (br t, J=10.8, 2H), 1.67-1.77 (m, 4H), 1.26-1.32 (m, 3H).

^{13}C NMR δ 166.6, 158.8, 152.4, 144.0, 136.5, 134.4, 129.4, 128.3, 127.5, 124.9, 122.9, 113.2, 111.4, 61.5, 56.2, 52.6, 34.3, 33.4, 30.7, 22.0.

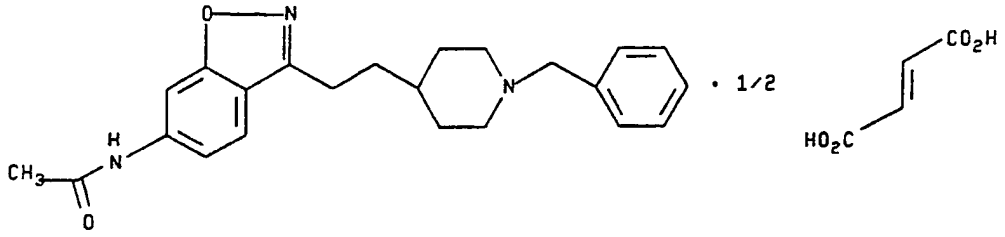
HRMS Calc'd (free base) 350.1992. Found: 350.1984.

IR (KBr) 1705, 1531, 1266, 756, 642 cm^{-1}.

Calc'd for $C_{22}H_{26}N_2O_2 \cdot C_4H_4O_4$:C, 66.94; H, 6.48; N, 6.00. Found: C, 66.76; H, 6.31; N, 5.61.

Example 7

6-Acetamido-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole hemifumarate



a) 4-[2-[6-Acetamido-1,2-benzisoxazol-3-yl]ethyl]-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

Freshly prepared 1M LDA (11.0 mL, 11.0 mmol) was added dropwise and quickly to a cold (-78°C) solution of 6-N-acetyl-3-methylbenzisoxazole (1.0 g, 5.26 mol) in THF (50 mL). Immediately after addition was complete, a solution of 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester (1.71 g, 5.26 mmol) in THF (8 mL) was added all at once. The resulting yellow-orange solution was stirred for 30 minutes at -78°C. Saturated ammonium chloride (NH_4Cl) was added and the mixture was extracted with ethyl acetate (EtOAc) (3 times). The combined organic layer was washed with brine, dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated.

Purification by silica gel flash chromatography (20% → 50% EtOAc/CH_2Cl_2) gave the title compound (1.56 g, 76%) as a white solid.

M.p.: 142-143°C

^{1}H-NMR ($CDCl_3$) δ 8.76 (s, 1H), 8.05 (s, 1H), 7.48 (d, 1H, J=8.5Hz), 7.32 (dd, 1H, J=8.6Hz, J=1.5Hz), 4.06 (br d, 2H, J=11.5Hz), 2.94 (t, 2H, J=7.8Hz), 2.66 (br t, 2H, J=11.8 Hz), 2.20 (s, 3H), 1.69-1.80 (m, 4H), 1.41-1.47 (m, 1H), 1.44 (s, 9H), 1.12 (ddd, 2H, J=23.8 Hz, J=12.0Hz, J=3.9Hz).

b) 6-Acetamido-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole fumarate

Trifluoroacetic acid (TFA) (4 mL) was added dropwise to a cold (0°C) solution of the piperidine formed in step a (0.40 g, 1.03 mmol) in CH_2Cl_2 (8 mL). The resulting solution was stirred at 0°C for 30 min. Volatiles were removed under reduced pressure and excess TFA was removed by concentrating from toluene twice. The crude product was redissolved in CH_2Cl_2 (10 mL) and triethylamine (1.44 mL, 10.3 mmol) and benzyl bromide (0.184 mL, 1.55 mmol) was added. The resulting mixture was stirred for 6 hours at room temperature. The mixture was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (CH_2Cl_2 → 10% MeOH/CH_2Cl_2) gave the title compound (free base) (0.270 g, 69%) as a white solid.

The fumarate salt was prepared by adding a solution of fumaric acid (0.091 g, 0.788 mmol) in ethanol (EtOH) (5 mL) to a solution of the free base (0.270 g, 0.716 mmol) in CH_2Cl_2 (20 mL). After concentrating, the solid obtained was recrystallized from EtOH to give white needles. Yield: 0.17 g, 48%.

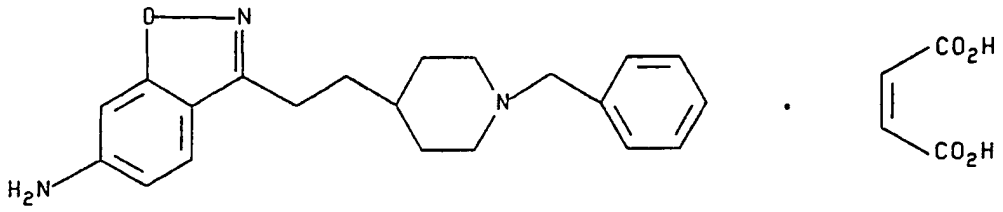
M.p. 225-226°C.

^{1}H NMR (DMSO-d_6) δ 10.37 (s, 1H), 8.13 (s, 1H), 7.76 (d, 1H, J=8.5), 7.25-7.36 (m, 6H), 6.59 (s, 2H), 3.54 (s, 2H), 2.83-2.96 (m, 4H), 2.10 (s, 3H), 2.01 (br t, 2H, J=11.1), 1.69-1.73 (m, 4H), 1.20-1.28 (m, 3H).

Calc'd for $C_{23}H_{27}N_3O_2 \cdot 1/2C_4H_4O_4 \cdot 1/4H_2O$: C, 68.24; H, 6.76; N, 9.55. Found: C, 68.35; H, 6.63; N, 9.35.

Example 8

6-Amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate



A mixture of 6-acetamido-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole (0.30 g, 0.79 mmol) in 1N HCl (10 mL) was heated to reflux for 30 min. The cooled reaction mixture was made basic with 10% NaOH and extracted with EtOAc (2 times). The combined organic layer was washed with brine and dried ($MgSO_4$), filtered, and concentrated to give the title compound (free base) (0.259 g, 98%) as an oil.

The mono maleate salt was prepared by adding a solution of maleic acid (0.099 g, 0.85 mmol) in EtOH (5 ml) to a solution of the free base (0.26, 0.77 mmol) in CH_2Cl_2 (3 mL). After concentrating, the residue was triturated with Et_2O to give a white powder. Yield: 0.29 g, 64%.

M.p. 173.0-173.5°C.

^1H NMR (DMSO-d_6) δ 7.41-7.47 (m, 6H), 6.58-6.63 (m, 2H), 6.06 (s, 2H), 5.87 (br s, 2H), 4.26 (s, 2H), 3.29-3.38 (m, 2H), 2.80-2.95 (m, 4H), 1.90 (br d, J=12.5, 2H) 1.25-1.80 (m, 5H).

^{13}C NMR (DMSO-d_6) 167.4, 164.8, 157.4, 151.9, 136.0, 131.2, 130.1, 129.5, 128.9, 121.9, 112.8, 110.7, 90.9, 59.3, 51.5, 32.6, 32.6, 28.6, 21.6.

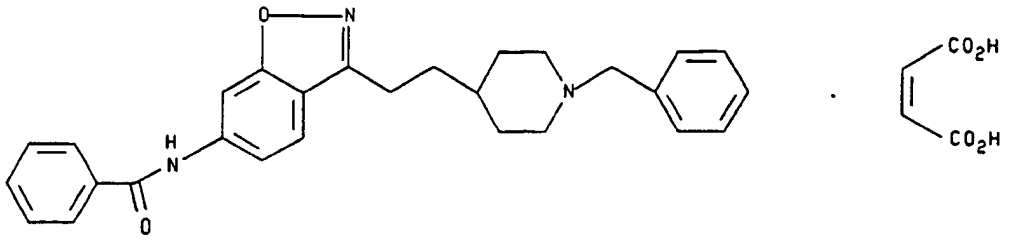
EIMS (no parent) 289, 268, 218, 190 (base).

IR (KBr) 3483, 3384, 2929, 2526, 1633, 1619, 1582, 1515, 1474, 1459, 1438, 1389, 1379, 1359, 877, 702 cm^{-1}.

Calc'd for $C_{21}H_{25}N_2O \bullet C_4H_4O_4$:C, 66.50; H, 6.47; N, 9.31. Found: C, 66.49; H, 6.43; N, 9.22.

Example 9

6-Benzamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate



a) 6-Benzamide-3-methyl-1,2-benzisoxazole

Benzoyl chloride (0.56 mL, 4.82 mmol) was added to a solution of 6-amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole (0.70 g, 4.72 mmol), triethylamine (1.35 mL, 9.69 mmol), and 4-dimethylaminopyridine (0.07 g, 0.57 mmol) in CH_2Cl_2 (30 mL). The resulting mixture was stirred overnight at room temperature. The heterogenous mixture was concentrated, and the solid obtained was collected and washed with water and ether and air-dried to give the title compound (1.02 g, 86%) as an off-white solid. A small sample was purified by recrystallization from EtOH to give pure white flakes.

M.p.: 213-214°C.

^{1}H-NMR (DMSO-d_6) δ 10.6 (s, 1H), 8.30 (s, 1H), 7.98 (d, 2H, J=6.9Hz), 7.80 (d, 1H, J=8.6Hz), 7.68 (d, 1H, J=8.8Hz), 7.52-7.63 (m, 3H), 2.53 (s, 3H).

b) 4-[2-[6-Benzamide-1,2-benzisoxazole-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

The procedure described in Example 7a was followed using the benzamide formed in step a (1.0 g, 3.96 mmol), 1M LDA (7.95 mL, 7.95 mmol), and 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester (1.30 g, 4.00 mmol) in dry THF (50 mL), except that after addition of reagents, the mixture was stirred at -78°C for 1.5 hours. After purification by chromatography (30% → 50% EtOAc/hexanes), the title compound (1.54 g, 87%) was obtained as a pale yellow solid. A small sample was

purified by recrystallization (CH_2Cl_2/Et_2O) to give a white solid.

M.p.: 177-178.5°C

^{1}H-NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.15 (s, 1H), 7.86 (d, 2H, J=7.4Hz), 7.39-7.53 (m,5H), 4.03 (br d, 2H, J=12.7Hz), 2.92 (t, 2H, J=8.0Hz), 2.50-2.73 (m, 2H), 1.60-1.80 (m, 4H), 1.40-1.45 (m, 1H), 1.41 (s, 9H), 1.13 (ddd, 2H, J=24.0 Hz, J=12.2Hz, J=3.8Hz).

c) 6-Benzamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole maleate

Trifluoroacetic acid (TFA) (8.4 mL) was added dropwise to a cold (0°C) solution of the piperidine formed in step b (0.70 g, 1.56 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred at 0°C for 30 min. Volatiles were removed under reduced pressure and excess TFA was removed by concentrating from toluene twice. The crude product was dissolved in THF (10 mL) and triethylamine (2.1 mL, 15.1 mmol) followed by benzyl bromide (0.21 mL, 1.77 mmol) was added. The resulting mixture was diluted with ethyl acetate and stirred overnight at room temperature. The mixture was then washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (30% EtOAc/CH_2Cl_2 → 100% EtOAc) gave the title compound (free base) (0.280 g, 41%) as a pale yellow solid.

The maleate salt was prepared by adding a solution of maleic acid (0.081 g, 0.702 mmol) in EtOH (5 mL) to a solution of the free base (0.280 g, 0.638 mmol) in CH_2Cl_2 (20 mL). After concentrating, the solid obtained was recrystallized from EtOH/CH_2Cl_2 to give a white solid. Yield: 0.208 g, 59%.

M.p. 181.5-183.0°C.

^{1}H NMR (DMSO-d_6) δ 10.65 (s, 1H), 8.31 (s, 1H), 7.98 (d, J=7.2, 2H), 7.85 (d, J=8.6, 1H), 7.48-7.71 (m, 9H), 6.03 (s, 2H), 4.25 (br s, 2H), 3.20-3.60 (m, 4H), 2.89-3.02 (t, @ 2.99, J=7.5 and m, 4H), 1.40-1.97 (m, 7H).

^{13}C NMR (DMSO-d_6) δ 167.2, 166.2, 163.0, 158.1, 141.5, 135.9, 134.6, 132.0, 131.2, 129.5, 128.9, 128.5, 127.8,

121.9, 117.01, 116.8, 99.9, 59.5, 51.7, 32.8, 32.5, 28.8, 21.7.

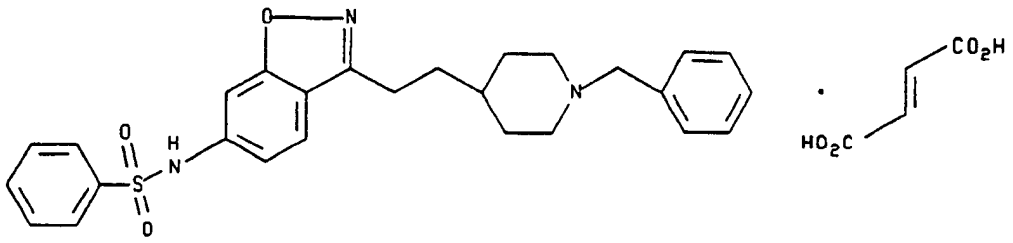
EIMS 439.2, 422.2 (100), 383, 348, 293, 185.

IR (KBr) 2934, 2919, 1657, 1610, 1579, 1536, 1499, 1491, 1462, 1453, 1352 cm^{-1}.

Calc'd for $C_{28}H_{29}N_3O_2 \bullet C_4H_4O_4$:C, 69.17; H, 5.99; N, 7.56. Found: C, 68.81; H, 5.90; N, 7.49.

Example 10

6-Benzenesulfonamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole fumarate



a) 6-Benzenesulfonamide-3-methyl-1,2-benzisoxazole

Benzenesulfonyl chloride (0.528 mL, 4.14 mmol) was added to a cold (0°C) solution of 6-amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole(0.613 g, 4.14 mmol) and pyridine (0.670 mL, 8.28 mmol) in CH_2Cl_2 (30 mL). After 1.3 hours, saturated sodium bicarbonate ($NaHCO_3$) was added and the resulting mixture was stirred overnight at room temperature. The organic layer was separated and washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatograph (5% EtOAc/CH_2Cl_2) gave the title compound (0.867 g, 83%) as a white solid.

M.p.: 183-184°C.

^{1}H-NMR ($CDCl_3$) δ 10.9 (br s, 1H), 7.84 (d, 2H, J=6.7Hz), 7.68 (d, 1H, J=8.5Hz), 7.52-7.63 (m, 3H), 7.34 (d, 1H, J=1.5Hz), 7.11 (dd, 1H, J=8.5Hz, J=1.7Hz), 2.52 (s, 3H).

b) 4-[2-[6-Benzenesulfonamide-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester

The procedure described in Example 7a was followed using the benzenesulfonamide formed in step a (0.60 g, 2.08

mmol), 1M LDA (4.58 mL, 4.58 mmol), and 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1-dimethylethyl) ester (0.813 g, 2.50 mmol) in dry THF (70 mL), except that after addition of reagents, the mixture was stirred at -78°C for 10-15 min. After purification by chromatography (20% → 40% EtOAc/hexanes), the title compound (0.997 g, 99%) was obtained as a white foam.

M.p.: 66-67°C.

^{1}H-NMR ($CDCl_3$) δ 7.85 (dd, 2H, J=8.3Hz, J=1.6Hz), 7.35-7.57 (m,6H), 7.02 (dd, 1H, J=8.5Hz, J=1.6Hz), 4.11 (br d, 2H, J=13.2Hz), 2.94 (t, 2H, J=7.4Hz), 2.68 (br t, 2H, J=12.8Hz), 1.71-1.77 (m, 4H), 1.46 (s, 9H), 1.46-1.55 (m, 1H), 1.15 (ddd, 2H, J=23.6Hz, J=11.7Hz, J=3.9Hz).

c) 6-Benzenesulfonamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole fumarate

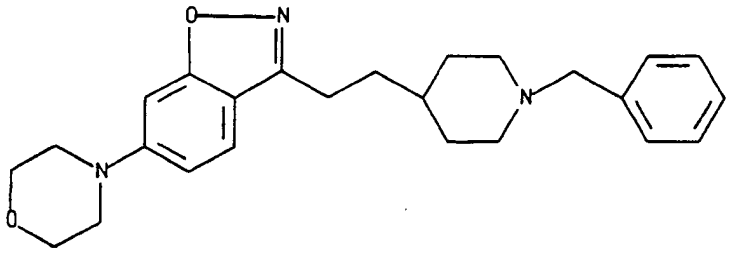
Trimethylsilyl trifluoromethanesulfonate (1.30 mL, 6.76 mmol) was added dropwise to a cold (0°C) solution of the piperidine formed in step b (0.819 g, 1.69 mmol) and 2,6-lutidine (0.590 mL, 5.07 mmol) in CH_2Cl_2 (17 mL). After 1.5 hours, saturated sodium bicarbonate ($NaHCO_3$) was added and the resulting mixture was stirred at room temperature for 15 min. The white precipitate formed was collected by filtration and redissolved in water at pH 2. This acidic aqueous layer was extracted with CH_2Cl_2 (2 times) and EtOAc (1 time). All organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The crude white solid obtained was suspended in THF (30 mL) and DMF (50 mL), and triethylamine (0.40 mL, 2.86 mmol) and benzyl bromide (0.22 mL, 1.86 mmol) were added. The resulting heterogenous mixture was stirred at room temperature for 24 hours (with time a more homogenous mixture was obtained). The mixture was concentrated, and CH_2Cl_2 was added to the residue. The organic layer was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (CH_2Cl_2 → 5% MeOH/CH_2Cl_2) gave the title compound (free base) (0.334 g, 49%) as a white foam.

The fu: rate salt was prepared by adding a solution of fumaric acid (0.040 g, 0.345 mmol) in EtOH (3 mL) to a solution of the free base (0.150 g, 0.315 mmol) in CH_2Cl_2 (6 mL). After concentrating, the residue was triturated with Et_2O to give a white solid. Yield: 0.151 g, 81%.

^1H NMR (DMSO-d_6) δ 7.82 (d, 2H, J=7.0), 7.70 (d, 1H, J=8.6), 7.51-7.60 (m, 3H), 7.27-7.32 (m, 6H), 7.07 (dd, 1H, J_1=8.6, J_2=1.6), 6.59 (s, 2H), 3.55 (s, 2H), 2.82-2.90 (m, 4H), 2.03 (br t, 2H, J=11.5), 1.61-1.70 (m, 4H), 1.20-1.25 (m, 3H).

Example 11

6-(4-Morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole



a) 3-Methyl-6-(4-morpholinyl)-1,2-benzisoxazole

A mixture of 6-amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole (0.230 g, 1.55 mmol), ß, ß'-dibromodiethyl ether (0.397 g, 1.71 mmol), and diisopropylethyl amine (Hunig's base, 0.648 mL, 3.72 mmol) in toluene (2.5 mL) was heated at 120°C for 15 hours. The cooled reaction mixture was diluted with EtOAc and washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. Two additional separate reactions using 6-amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole (0.050 g, 0.34 mmol, and 0.150 g, 1.01 mmol) were carried out in the same manner. Crude product from the three reactions was combined and purified by silica gel flash chromatography (1% MeOH/CH_2Cl_2) to give the title compound (0.499 g, 79% combined yield) as a pale yellow solid. A small sample was further purified by recrystallization (EtOAc/hexanes) to give a white solid.

M.p.: 138.5-139.5°C.

^{1}H-NMR ($CDCl_3$) δ 7.46 (d, 1H, J=8.7Hz), 6.95 (dd, 1H, J=8.7Hz, J=2.0Hz), 6.90 (d, 1H, J-1.9Hz), 3.88 (t, 4H, J=4.9Hz), 3.27 (t, 4H, J=4.8Hz), 2.52 (s, 3H).

b) 4-[2-[6-(4-Morpholinyl)-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester

The procedure described in Example 7a was followed using the morpholino derivative formed in step a (0.369 g, 1.69 mmol), 1M LDA (1.86 mL, 1.86 mmol), and 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester (0.605 g, 1.86 mmol) in dry THF (8 mL). Another reaction with the above morpholino derivative (0.100 g, 0.46 mmol) was also carried out. Crude product from both reactions was combined and after purification by chromatography (5% → 40% EtOAc/hexanes), the title compound (0.477 g, 53%) was obtained as a white solid. A small sample was further purified by recrystallization (EtOAc/hexanes) to give a white solid.

M.p.: 164-165°C.

^{1}H-NMR ($CDCl_3$) δ 7.46 (d, 1H, J=8.6Hz), 6.92-6.97 (m, 2H), 4.02-4.15 (m, 2H), 3.89 (t, 4H, J=4.9Hz), 3.27 (t, 4H, J=4.9Hz), 2.95 (t, 2H, J-7.8Hz), 2.7 (br t, 2H, J=12.1Hz), 1.74-1.80 (m, 4H), 1.46-1.56 (m, 1H), 1.46 (s, 9H), 1.10-1.22 (m, 2H).

c) 6-(4-Morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl-1,2-benzisoxazole

Trifluoroacetic acid (TFA) (5 mL) was added to a cold (0°C) solution of the piperidine formed in step b (0.40 g, 0.96 mmol) and thioanisole (1.13 mL, 9.60 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at 0°C for 30 min. Volatiles were removed under reduced pressure and 1N sodium hydroxide (NaOH) was added to the residue. The aqueous layer was extracted with EtOAc (2 times) and the combined organic layer was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. The yellow oil obtained was redissolved in CH_2Cl_2 (10 mL), and triethylamine (0.267

mL, 1.92 mmol) and benzyl bromide (0.148 mL, 1.25 mmol) were added. The resulting mixture was stirred overnight at room temperature. The mixture was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (CH_2Cl_2 → 10% MeOH/CH_2Cl_2) gave the title compound (0.285 g, 73%) as a white solid. A small sample was further purified by recrystallization (EtOH) to give a white solid.

M.p. 129-130°C.

^1H NMR ($CDCl_3$) δ 7.44 (d, J=8.7, 1H), 7.23-7.30 (m, 5H), 6.89-6.93 (m, 2H), 3.87 (t, J=4.8, 4H), 3.47 (s, 2H), 3.25 (t, J=4.8, 4H), 2.85-2.94 (m, 4H), 1.92 (br t, J=10.8, 2H), 1.72-1.79 (m, 4H), 1.21-1.31 (m, 3H).

^{13}C NMR 165, 158, 153.4, 138.8, 129.2, 128.1, 126.9, 121.3, 113.3, 94.5, 66.7, 63.5, 53.7, 49.1, 35.3, 34.4, 32.1, 22.7.

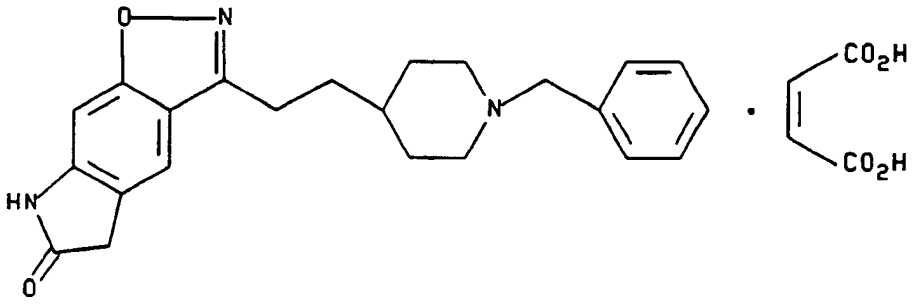
IR (KBr) 3020, 2920, 1950, 1895, 1815, 1722, 1620, 1450, 1250, 1122, 738 cm^{-1}.

Calc'd for $C_{25}H_{31}N_3O_2$: C, 74.04; H, 7.70; N, 10.36. Found: C, 73.75; H, 7.69; N, 10.36.

Example 12

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-

pyrrolo [4,5-f]-1,2-benzisoxazol-6-one maleate



a) 5-Acetyl-1,3-dihydro-6-hydroxy-2H-indol-2-one

Acetyl chloride (4.09 mL, 0.0575 mol) was added to a slurry of aluminum trichloride ($AlCl_3$) (35.36 g, 0.265 mol) in carbon disulfide (CS_2) (250 mL). After 2-3 min, 6-

methoxyoxindole (7.22 g, 0.0442 mol) was added. The resulting mixture was heated to reflux for 2.5 hours. (A black tar developed with time). Excess solvent was decanted and ice water was added carefully to the residue. The resulting mixture was stirred overnight. The pale yellow solid obtained was collected, washed with water and dried under high vacuum to give the title compound (7.32 g, 87%).

^{1}H-NMR (DMSO-d_6) δ 13.0 (s, 1H), 10.8 (s, 1H), 7.70 (s, 1H), 6.30 (s, 1H), 3.40 (s, 2H), 2.54 (s, 3H).

b) 5-Acetyl-1,3-dihydro-6-hydroxy-2H-indol-2-one, 5-oxime

An aqueous solution of hydroxylamine hydrochloride (8.26 g, 0.119 mol) and sodium acetate trihydrate (16.9 g, 0.124 mol) was a added to a mixture of the ketone formed in step a (9.88 g, 0.0517 mol) in EtOH (600 mL). The resulting mixture was heated to reflux for 20 hours. The hot reaction mixture was filtered and the solid collected was rinsed with EtOH. After drying, the title compound (10.11 g, 95%) was obtained as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ 12.0 (s, 1H), 11.4 (s, 1H), 10.5 (s, 1H), 7.29 (s, 1H), 6.35 (s, 1H), 3.38 (s, 2H), 2.20 (s, 3H).

c) 5-Acetyl-1,3-dihydro-6-hydroxy-2H-indol-2-one, 5-oxime acetate

A heterogenous mixture of the oxime formed in step b (7.15 g, 34.7 mmol) in acetic anhydride (55 mL) was heated at 80°C for 2 hours. The cooled reaction mixture was filtered and the solid collected was rinsed with water. After drying, the title compound (4.67 g, 54%) was obtained as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ 11.3 (s, 1H), 10.6 (s, 1H), 7.35 (s, 1H), 6.44 (s, 1H), 3.41 (s, 2H), 2.37 (s, 3H), 2.21 (s, 3H).

d) 5,7-Dihydro-3-methyl-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one

A mixture of the oxime acetate formed in step c (4.48 g, 18.0 mmol) and pyridine (14.6 mL, 180 mmol) in dimethylformamide (DMF) (660 mL) was heated at 125-130°C for 4 hours. The cooled reaction mixture was poured over water

and extracted with EtOAc (4 times). The combined organic layer was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (50% EtOAc/hexanes → 100% EtOAc) gave the title compound (2.20 g, 65%) as a pale yellow-orange solid.

M.p. (EtOAc): 264-265°C (dec).

^{1}H-NMR (DMSO-d_6) δ 10.8 (s, 1H), 7.60 (s, 1H), 6.98 (s, 1H), 3.57 (s, 2H), 2.47 (s, 3H).

e) 4-[2-[5,7-Dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one-3-yl]ethyl]-1-piperidinecarboxylic acid,1-(1,1-dimethylethyl)ester.

The procedure described in Example 7a was followed using the benzisoxazole formed in step d (2.33 g, 12.4 mmol), 1M LDA (40.9 mL, 40.9 mmol), and 4-iodomethyl-1-piperidine-carboxylic acid, 1-(1,1-dimethylethyl) ester (4.42 g, 13.6 mmol) in dry THF (500 mL), except that after addition of reagents, the mixture was stirred at -78°C for 4 hours. Purification by chromatography (20% → 30% EtOAc/CH_2Cl_2) gave recovered starting material (0.210 g, 9%) and the title compound (2.75 g, 58%) as an off-white solid.

^{1}H-NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.44 (s, 1H), 7.03 (s, 1H), 4.08-4.14 (m, 2H), 3.63 (s, 2H), 2.97 (t, 2H, J=7.8Hz), 2.69 (br t, 2H, J=12.8Hz), 1.74-1.84 (m, 4H), 1.46-1.55 (m, 1H), 1.46 (s, 9H), 1.18 (ddd, 2H, J=24.4Hz, J=12.1Hz, J=4.3Hz).

f) 5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one maleate

Trifluoroacetic acid (TFA)(3.3 mL) was added dropwise to a cold (0°C) solution of the piperidine formed in step e (0.50 g, 1.30 mmol) in CH_2Cl_2 (13 mL). After 30 min, the mixture was concentrated and excess TFA was removed by concentrating from toluene (2 to 3 times). The crude residue was dissolved in DMF (12.5 mL) and sodium carbonate (Na_2CO_3) (0.689 g, 6.50 mmol) and benzyl bromide (0.186 mL, 1.56 mmol) were added. The resulting mixture was stirred at

room temperature for 4 hours. The reaction was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in methylene chloride and washed with brine, and dried ($MGSO_4$), filtered, and concentrated. Purification by silica gel chromatography (CH_2Cl_2 → 10% methanol/CH_2Cl_2) gave the title compound (free base) (0.343 g, 70%) as a white solid.

The maleate salt was prepared by adding a solution of maleic acid (0.061 g, 0.528 mmol) in ethanol (EtOH) (1 mL) to a solution of the free base (0.180 g, 0.48 mmol) in CH_2Cl_2 (10 mL). After concentrating, the salt was purified by recrystallization from isopropanol to give an off-white solid. Yield: 0.173 g, 73%.

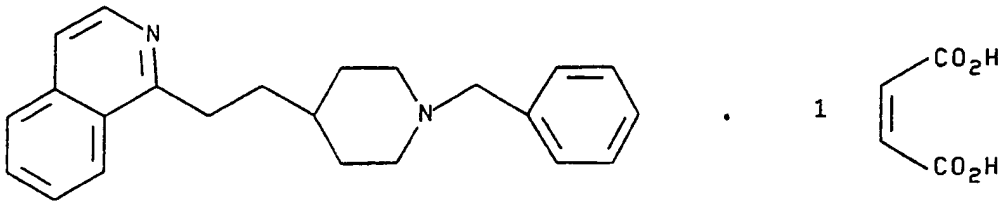
M.p. 194-195°C.

^1H NMR (DMSO-d_6) δ 10.82 (s, 1H), 7.65 (s, 1H), 7.48 (s, 5H), 7.00 (s, 1H), 6.03 (s, 1H), 4.24 (br s, 2H), 3.58 (s, 2H), 3.25-3.38 (m, 2H), 2.94 (t, 2H, J=7.6), 2.81-2.97 (m, 2H), 1.86-1.96 (m, 2H), 1.62-1.76 (m, 2H), 1.30-1.60 (m, 3H).

Calc'd for $C_{23}H_{25}N_3O_2 \bullet C_4H_4O_4$: C, 65.97; H, 5.95; N, 8.55. Found: C, 65.98; H, 6.04; N, 8.54.

Example 13

1-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]isoquinoline maleate



a) 4-[2-[1-Isoquinolyl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester

The procedure described in Example 7a was followed using 1-methyl isoquinoline (0.50 g, 3.49 mmol), 1M LDA (4.2 mL, 4.2 mmol), and 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl) ester (1.2 g, 3.84 mmol) in dry THF (45 mL) except that after addition of the reagents, the

mixture was stirred at -78°C for 1.75 hours. Purification by chromatography (30% EtOAc/toluene) gave the title compound (0.784 g, 66%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ 8.38 (d, 1H, J=5.8Hz), 8.08 (d, 1H, J=8.3Hz), 7.77 (d, 1H, J=8.0Hz), 7.62 (t, 1H, J=7.1Hz), 7.54 (t, 1H, J=7.1Hz), 7.46 (d, 1H, J=5.7Hz), 4.08 (br s, 2H), 3.25-3.30 (m, 2H), 2.67 (br t, 2H, J=12.3Hz), 1.73-1.81 (m, 4H), 1.49-1.63 (m, 1H), 1.42 (s, 9H), 1.17 (ddd, 2H, J=24.6Hz, J=12.1Hz, J=3.8Hz).

b) 1-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-isoquinoline maleate

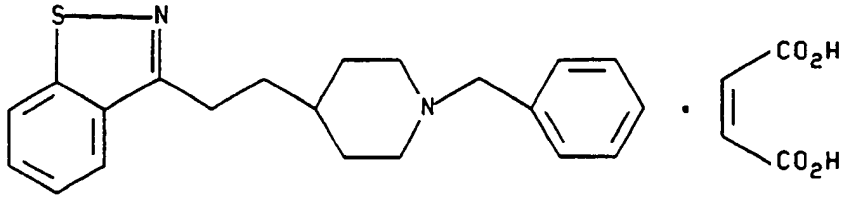
The procedure described in Example 1e was followed using the piperidine formed in step a (0.713 g, 2.10 mmol) and TFA (7 mL) in CH_2Cl_2 (14 mL), and triethylamine (2.9 mL, 21.0 mmol) and benzyl bromide (0.275 mL, 2.31 mmol) in CH_2Cl_2 (60 mL). After purification (CH_2Cl_2 → 5% MeOH/CH_2Cl_2), the title compound (free base) (0.26 g, 38%) was obtained as a pale yellow oil.

The mono maleate salt was prepared by adding a solution of maleic acid (0.10 g, 0.867 mmol) in EtOH (3 mL) to a solution of the free base (0.26 g, 0.788 mmol) in CH_2Cl_2 (7 mL). After concentrating, the salt was purified by recrystallization [cold (0°) EtOAc] to give an off-white solid. Yield: 0.195 g, 56%.

^{1}H NMR (DMSO-d_6) δ 8.39 (d, 1H, J=5.7), 8.26 (d, 1H, J=8.3), 7.97 (d, 1H, J=8.1), 7.77 (t, 1H, J=7.4), 7.66-7.71 (m, 2H), 7.49 (s, 5H), 6.05 (s, 2H), 4.28 (br s, 2H), 3.27-3.32 (m, 2H), 2.87-2.90 (m, 2H), 1.76-2.03 (m, 6H), 1.55-1.69 (m, 1H), 1.33-1.46 (m, 2H).

Example 14

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisothiazole maleate



a) 4-[2-[1,2-Benzisothiazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester.

The procedure described in Example 1d was followed using 3-methyl-1,2-benzisothiazole (0.50 g, 3.35 mmol), 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (1.20 g, 3.69 mmol), and 1M lithium diisopropylamide (LDA) (3.35 mL, 3.35 mmol) in dry THF (100 mL). After purification, the title compound (0.582 g, 50%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 7.91-7.96 (m, 2H), 7.43-7.52 (m, 2H), 4.05-4.14 (m, 2H), 3.15 (t, 2H, J=7.9Hz), 2.69 (br t, 2H, J=12.1Hz), 1.74-1.88 (m, 4H), 1.46-1.60 (m, 1H), 1.46 (s, 9H), 1.29-1.10 (m, 2H).

b) 3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisothiazole maleate

The procedure described in Example 1e was followed using the piperidine formed in step a (0.102 g, 0.29 mmol) and trifluoroacetic acid (TFA) (0.75 mL) in methylene chloride (CH_2Cl_2) (3 mL), and triethylamine (0.202 mL, 1.45 mmol) and benzyl bromide (0.038 mL, 0.32 mmol) in methylene chloride (CH_2Cl_2) (3 mL). After purification, the title compound (free base) (0.058 g, 62%) was obtained as a clear oil.

The maleate salt was prepared by adding a solution of maleic acid (0.020 g, 0.17 mmol) in EtOH (3 mL) to a solution of the free base (0.058 g, 0.17 mmol) in CH_2Cl_2 (3 mL). The resulting mixture was concentrated and the residue was triturated with Et_2O. The white solid obtained was filtered and collected to give the title compound (0.077 g, 96%).

^{1}H-NMR ($CDCl_3$) δ 8.14-8.21 (m, 2H), 7.63 (t, J=7.4, 1H), 7.50-7.55 (m, 6H), 6.04 (s, 2H), 4.26 (br s, 2H), 3.35 (br s, 2H), 3.15 (t, J=7.6, 2H), 2.80-2.92 (m, 2H), 1.92-2.00 (m, 2H), 1.78-1.88 (m, 2H), 1.54-1.65 (m, 1H), 1.35-1.45 (m, 2H).

M.p.: 175-176°C.

^{13}C-NMR (DMSO-d_6) δ 167.3, 166.2, 151.6, 136.0, 134.2, 131.2, 130.1, 129.5, 128.9, 127.9, 124.9, 123.6, 120.6, 59.4, 51.6, 32.5, 33.5, 28.9, 27.8.

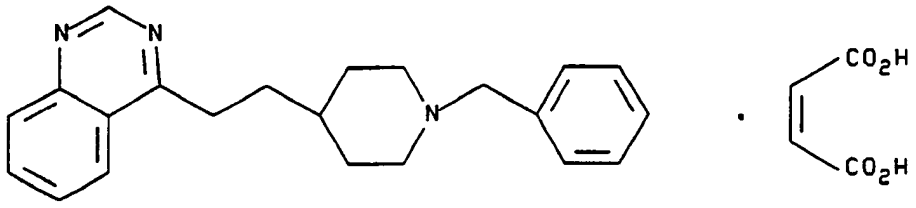
IR (KBr) 3030, 2910, 2350, 1700, 1575, 1445, 1350 cm^{-1}.

EIMS: 336.2 (M+, free base), 319.1, 245.1, 185.1, 172.1, 91.0 (base).

Anal. Calcd. for $C_{21}H_{24}N_2S \bullet C_4H_4O_4$: C, 66.35; H, 6.24; N, 6.19. Found: C, 66.21; H, 5.93; N, 6.03.

Example 15

4-[2-[1-(Phenylmethyl)-4-piperidyl]ethyl]-1,3-quinazoline maleate



a) 4-[2-[1,3-Quinazol-4-yl]ethyl]-1-piperidine-carboxylic acid, 1-(1,1-dimethylethyl)ester

Freshly made 1M LDA (4.2 mL, 4.2 mmol) was added to a solution of 4-methyl-1,3-quinazoline (0.60 g, 4.2 mmol) in THF (35 mL) at 0°C. To the yellow solution obtained, was added neat trimethylsilyl chloride (0.53 mL, 4.2 mmol). The ice bath was removed and the reaction was allowed to stir for 3 min. The mixture was re-cooled to 0°C, and a second equivalent of 1M LDA (4.2 mL, 4.2 mmol) was added. Next, a solution of 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (1.49 g, 4.6 mmol) in THF (10 mL) was added and stirring was continued at 0°C for 1 hour. Dilute HCl (1 N) was added and the mixture was stirred at room temperature for 30 min. The reaction was made basic by addition of 1N NaOH and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (20→50% EtOAc-hexanes) gave the title compound (0.466 g, 33%) as an oil.

^{1}H-NMR ($CDCl_3$) δ 9.21 (s, 1H), 8.12 (d, 1H, J=7.7Hz), 8.05 (d, 1H, J=8.4Hz), 7.90 (t, 1H, J=7.8 Hz), 7.65 (t, 1H, J=7.7Hz), 4.08-4.17 (m, 2H), 3.32 (t, 2H, J=8.3Hz), 2.72 (br t, 2H, J=12.1Hz), 1.78-1.90 (m, 4H), 1.57-1.59 (m, 1H), 1.47 (s, 9H), 1.18-1.29 (m, 2H).

b) 4-[2-[1-(Phenylmethyl)-4-piperidyl]ethyl]-1,3-quinazoline maleate

The procedure described in Example 1e was followed with the piperidine obtained in step a (0.429 g, 1.26 mmol) and TFA (3.5 mL) in CH_2Cl_2 (13 mL), and triethylamine (0.88 mL, 6.3 mmol) and benzyl bromide (0.17 mL, 1.39 mmol) in CH_2Cl_2 (22 mL). After purification by chromatography (CH_2Cl_2→10% MeOH-CH_2Cl_2), the title compound, free base (0.179 g, 43%) was obtained as a colorless oil.

The maleate salt was prepared by adding a solution of maleic acid (0.052 g, 0.45 mmol) in Et_2O (10 mL) to a solution of the free base (0.135 g, 0.41 mmol) in Et_2O (200 mL). The white solid obtained was collected by filtration to give the title compound (0.103 g, 56%).

M.p.: 121-122°C.

^{1}H-NMR (DMSO-d_6) δ 9.16 (s, 1H), 8.33 (d, 1H, J=8.4Hz), 7.98-8.01 (m, 2H), 7.72-7.78 (m, 1H), 7.43 (s, 5H), 6.02 (s, 2H), 4.08 (br s, 2H), 3.32 (t, 2H, J=7.7Hz), 3.15-3.35 (m, 2H), 2.60-2.80 (m, 2H), 1.89-1.94 (m, 2H), 1.76-1.79 (m, 2H), 1.30-1.60 (m, 3H).

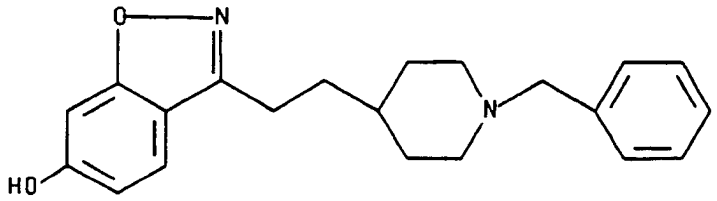
IR (KBr) 3037, 2923, 1705, 1571, 1386 cm^{-1}.

EIMS: 331 (M+, free base), 318, 248, 143, 77 (base).

Anal. Calcd. for $C_{22}H_{25}N_3 \cdot C_4H_4O_4$: C, 69.78; H, 6.53; N, 9.39. Found: C, 69.46; H, 6.61; N, 9.26.

Example 16

6-Hydroxy-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole



A mixture of 6-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole (0.1.1 g, 0.288 mmol) in 48% aqueous HBr (10 mL) was heated at 110°C for 16 hours. The mixture was made basic by addition of saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (3→6% MeOH-CH_2Cl_2) gave the title compound (0.055 g, 57%) as a white solid.

M.p.: 148-149°C.

^{1}H-NMR ($CDCl_3$) δ 7.70 (br s, 1H), 7.27-7.37 (m, 6H), 6.74-6.80 (m, 2H), 3.63 (s, 2H), 3.04 (br d, 2H, J=10.8Hz), 2.88 (t, 2H, J=7.7Hz), 2.05-2.20 (m, 2H), 1.65-1.95 (m, 4H), 1.30-1.60 (m, 3H).

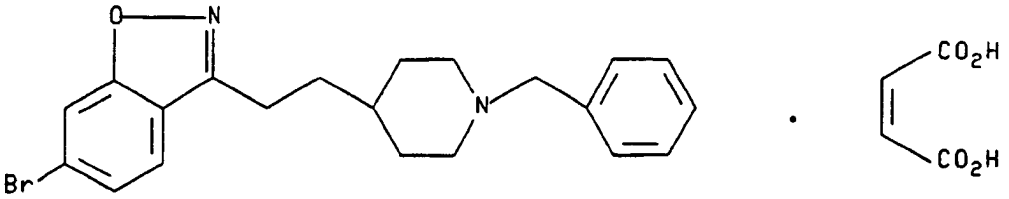
IR (KBr) 3080, 3040, 2945, 1624, 1437, 1384 cm^{-1}.

EIMS: 336.2 (M+), 319.2, 255.0, 185.1, 91.1 (base).

HRMS calcd. for $C_{21}H_{24}N_2O_2$: 336.18382. Found: 336.18187.

Example 17

6-Bromo-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole maleate



a) 4-[2-[6-Bromo-1,2-benzisoxazol-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

The procedure described in Example 1d was followed with 6-bromo-3-methyl-1,2-benzisoxazole (1.02 g, 4.81 mmol), 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (1.72 g, 5.29 mmol), and 1M LDA (5.30 mL, 5.30 mmol) in dry THF (40 mL), except that after addition of reagents, the mixture was stirred at -78°C for 1.5 hours. After purification, the title compound (0.697 g, 35%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.52 (d, 1H, J=7.2Hz), 7.45 (d, 1H, J=7.2Hz), 4.11 (br d, 2H, J=14.3Hz), 3.02 (t, 2H, J=7.2Hz), 2.70 (dt, 2H, J=12.9Hz, J=3.6Hz), 1.70-1.85 (m, 4H), 1.49 (s, 9H), 1.45-1.55 (m, 1H), 1.09-1.29 (m, 2H).

b) 6-Bromo-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate

The procedure described in Example 1e was followed with the piperidine formed in step a (0.398 g, 0.972 mmol) and TFA (4 mL) in CH_2Cl_2 (26 mL), and triethylamine (1.6 mL, 11.8 mmol) and benzyl bromide (0.155 mL, 1.3 mmol) in CH_2Cl_2 (12 mL). Another reaction with the above piperidine (0.102g, 0.249 mmol) was also carried out. Crude product from both reactions was combined and after purification, the title compound, free base (0.021 g, 4%) was obtained as a tan solid.

The maleate salt was prepared by adding a solution of maleic acid (0.023 g, 0.198 mmol) in EtOH (5 mL) to a solution of the free base (0.072 g, 0.18 mmol) in CH_2Cl_2 (6 mL). After concentration, the residue was recrystallized from EtOH to give the title compound (0.035 g, 38%) as a white solid.

M.p.: 156.8-157.5°C.

^{1}H-NMR (DMSO-d_6) δ 8.08 (s, 1H), 7.87 (d, 1H, J=8.4Hz), 7.58 (d, 1H, J=8.5Hz), 7.47 (s, 5H), 6.03 (s, 2H), 4.23 (br s, 2H), 3.25-3.40 (m, 2H), 3.02 (t, 2H, J=7.5Hz), 2.80-2.95 (m, 2H), 1.88-2.00 (m, 2H), 1.70-1.80 (m, 2H), 1.30-1.60 (m, 3H).

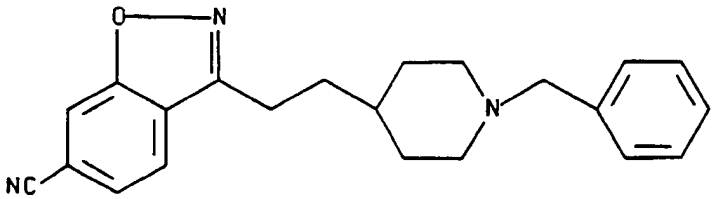
^{13}C-NMR (DMSO-d_6) δ 167.2, 162.8, 158.6, 136.0, 131.1, 129.5, 128.9, 127.0, 124.0, 123.7, 120.6, 113.1, 59.6, 51.9, 32.7, 28.9, 21.6.

EIMS: 398 (M+), 381, 309, 252, 200, 185 (base), 172, 91.

HRMS calc'd for $C_{21}H_{23}BrN_2O$: 398.0994. Found: 398.0941.

Example 18

6-Cyano-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole



A solution of $NaNO_2$ (0.112 g, 1.62 mmol) in H_2O (4 mL) was added to a solution of 6-amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole (0.534 g, 1.59 mmol) in 28% HCl (20 mL) kept at 0°C. The resulting mixture was neutralized to pH 7 by cautious addition of solid Na_2CO_3. The neutral mixture was added in portions to a well-stirred mixture of toluene (75 mL), ice, and a freshly prepared solution of CuCN (Organic Synthesis, Coll. Vol. I, p. 514; $CuSO_4$: 0.318 g, 1.99 mmol). The mixture obtained was kept at 0°C for 30 minutes, then at room temperature for 2 hours, and finally, heated at 50°C for 5 minutes. The mixture was extracted with ethyl acetate and the organic phase was washed with H_2O, brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (3% MeOH-CH_2Cl_2) gave the title compound (0.236 g, 43%) as a pale orange solid. Recrystallization (EtOH-hexanes) of a small sample gave the title compound as an off-white solid.

M.p.: 113-114.5°C.

^{1}H-NMR ($CDCl_3$) δ 7.89 (s, 1H), 7.77 (d, 1H, J=8.4Hz), 7.57 (d, 1H, J=8.7Hz), 7.24-7.33 (m, 5H), 3.51 (s, 2H), 3.04

(t, 2H, J=7.9Hz), 2.92 (br d, 2H, J=11.2Hz), 1.97 (br t, 2H, J=10.7Hz), 1.74-1.85 (m, 4H), 1.26-1.40 (m, 3H).

^{13}C-NMR ($CDCl_3$) δ 161.7, 158.8, 129.2, 128.2, 127.0, 126.3, 125.1, 122.5, 118.1, 114.5, 113.2, 63.4, 53.6, 35.2, 34.0, 32.0, 22.6.

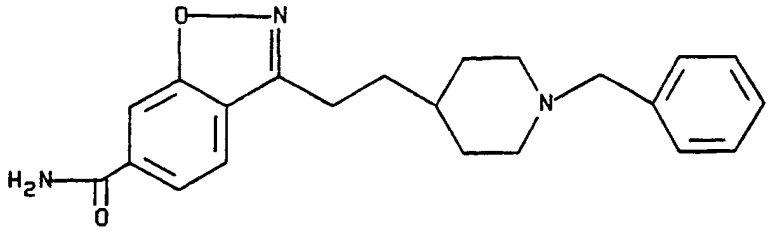
IR ($CHCl_3$) 2830, 2720, 2160, 1600, 1425, 1385 $^{cm-1}$.

FABMS: 346 (M+ + 1), 309, 275, 239, 155, 119 (base).

HRMS calc'd for $C_{22}H_{23}N_3O$: 345.1842. Found: 345.1826.

Example 19

6-Carboxamide-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole



Powdered KOH (0.150 g, 2.68 mmol) was added to a mixture of 6-cyano-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole (0.250 g, 0.724 mmol) in t-BuOH (10 mL). The resulting mixture was heated at 85°C for 20 minutes. The cooled reaction mixture was poured over brine and extracted with CH_2Cl_2. The organic phase was washed with 10% NaOH, brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by recrystallization (EtOAc-hexanes) to give the title compound (0.114 g, 43%) as a white solid.

M.p.: 181-182°C.

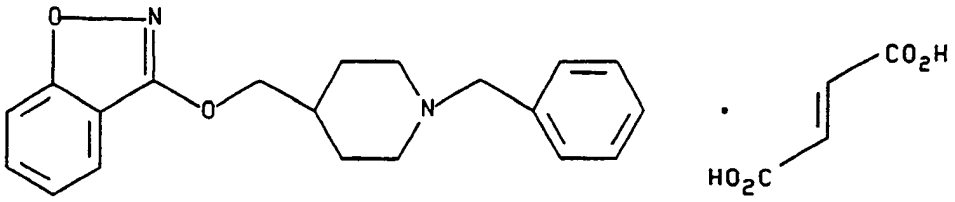
^{1}H-NMR (DMSO-d_6) δ 8.20 (br s, 1H, -NH), 8.15 (s, 1H), 7.97 (d, 1H, J=8.4Hz), 7.87 (d, 1H, J=8.1Hz), 7.64 (br s, 1H-NH), 7.22-7.31 (m, 5H), 3.42 (s, 2H), 3.02 (t, 2H, J=7.8Hz), 2.78 (br d, 2H, J=11.5Hz), 1.87 (br t, 2H, J=10.9Hz), 1.69-1.73 (m, 4H), 1.22-1.26 (m, 3H).

^{13}C-NMR (DMSO-d_6) δ 167.1, 162.0, 158.9, 138.9, 136.3, 128.7, 126.8, 126.8, 123.3, 122.9, 122.0, 108.7, 62.5, 53.2, 34.9, 33.7, 31.6, 22.0.

FABMS: 346 [(M^+ + 1), base], 321, 272, 185, 172.

Example 20

3-[(1-Phenylmethyl-4-piperidyl)methoxy]-1,2-benzisoxazole fumarate



a) 4-[(1,2-Benzisoxazol-3-yl)oxymethyl]-1-piperidine-carboxylic acid, 1-(1,1-dimethylethyl)ester

NaH (60% mineral oil dispersion, 0.941 g, 23.53 mmol) was added in portions to a solution of 4-hydroxymethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (4.82 g, 22.41 mmol) in DMF (220 mL) at 0°C. After 10 minutes, the reaction was warmed to room temperature and 3-chloro-1,2-benzisoxazole (3.44 g, 22.41 mmol) was added. The mixture obtained was heated at 115°C for 16 hours. The reaction mixture was diluted with EtOAc and washed with H_2O (4x), brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (10% EtOAc-hexanes) gave the title compound (4.16 g, 56%) as a white solid.

M.p.: 103-104.5°C.

^{1}H-NMR ($CDCl_3$) δ 7.61 (d, 1H, J=7.9Hz), 7.48-7.54 (m, 1H), 7.41 (d, 1H, J=8.5Hz), 7.22-7.27 (m, 1H), 4.28 (d, 2H, J=6.5Hz), 4.16 (br d, 2H, J=13.3Hz), 2.75 (dt, 2H, J=13.2Hz, J=2.6Hz), 2.04-2.13 (m, 1H), 1.83 (br d, 2H, J=13.7Hz), 1.45 (s, 9H), 1.30 (ddd, 2H, J=24.9Hz, J=12.5Hz, J=4.2Hz).

b) 3-[(1-Phenylmethyl-4-piperidyl)methoxy]-1,2-benzisoxazole fumarate

Trifluoroacetic acid (TFA) (10 mL) was added dropwise to a solution of piperidine formed in step a (0.827 g, 2.49 mmol) in CH_2Cl_2 (25 mL) at 0°C. The resulting mixture was stirred at 0°C for 20 minutes. The mixture was concentrated, and excess TFA was removed by concentrating from toluene. The residue was partitioned between CH_2Cl_2 and

saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product (0.192 g, 0.827 mmol) was dissolved in CH_2Cl_2 (8 mL), and triethylamine (0.58 mL, 4.13 mmol) followed by benzyl bromide (0.128 mL, 1.07 mmol) was added. The mixture was stirred overnight (18 hours) at room temperature. The reaction was washed with H_2O, brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (5% MeOH-CH_2Cl_2) gave the title compound, free base (0.199 g, 25%) as an off-white solid.

The fumarate salt was prepared by adding fumaric acid (0.074 g, 0.633 mmol) dissolved in the minimum amount of EtOH to a solution of the free base (0.186 g, 0.58 mmol) in CH_2Cl_2 (6 mL). After concentrating, the crude salt was purified by recrystallization (EtOH-Et_2O) to give the title compound (0.134 g, 53%) as an off-white solid.

M.p.: 163-164°C.

^{1}H-NMR (DMSO-d_6) δ 7.74 (d, 1H, J=7.8Hz), 7.61-7.69 (m, 2H), 7.26-7.41 (m, 6H), 6.60 (s, 2H), 4.28 (d, 2H, J=6.4Hz), 3.65 (s, 2H), 2.97 (br d, 2H, J=11.4 Hz), 2.20 (br t, 2H, J=11.7Hz), 1.90-2.05 (m, 1H), 1.81 (brd, 2H, J=12.8Hz), 1.38-1.49 (m, 2H).

^{13}C-NMR (DMSO-d_6) δ 166.5, 166.1, 163.3, 137.0, 134.3, 131.1, 129.3, 128.3, 127.3, 123.6, 120.8, 113.5, 110.3, 74.2, 61.7, 52.2, 34.7, 27.6.

IR (KBr) 2980, 2550, 1706, 1650, 1616, 1573, 1447, 1374 cm^{-1}.

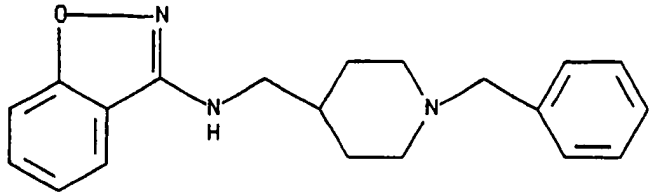
EIMS: 305, 185, 172, 91 (base).

HRMS calc'd. for $C_{20}H_{22}N_2O_2$ (freebase): 322.1682. Found: 322.1719.

Anal. Calc'd. for $C_{20}H_{22}N_2O_2 \cdot C_4H_4O_4 \cdot 0.75H_2O$:C, 63.78; H, 6.13; N, 6.20. Found: C, 63.88; H, 5.85; N, 6.14.

Example 21

3-[(1-Phenylmethyl-4-piperidyl)methylamino]-1,2-benzisoxazole



A mixture of 3-chloro-1,2-benzisoxazole (0.238 g, 1.55 mmol), 4-aminomethyl-1-phenylmethyl piperidine (0.316 g, 1.55 mmol), and K_2CO_3 (0.214 g, 1.55 mmol) in DMSO (10 mL) was heated at 150°C for 20 hours. The cooled reaction mixture was diluted with EtOAc (75 mL) and poured over H_2O (200 mL). The organic phase was separated and washed with brine, dried ($MgSO_4$), filtered, and concentrated. The brown oil obtained was purified by silica gel flash chromatography (4% MeOH-CH_2Cl_2) to give the title compound (0.084 g, 17%) as pale yellow oil.

^{1}H-NMR ($CDCl_3$): δ 7.44-7.50 (m, 2H), 7.38 (d, 1H, J=8.8Hz), 7.16-7.31 (m, 6H), 4.35-4.42 (m, 1H, -NH-), 3.51 (s, 2H), 3.33 (t, 2H, J=6.2Hz), 2.92 (br d, 2H, J=11.5Hz), 1.99 (t, 2H, J=11.6Hz), 1.77 (br d, 2H, J=12.7Hz), 1.75-1.80 (m, 1H), 1.33-1.45 (m, 2H).

^{13}C-NMR ($CDCl_3$) δ 162.8, 158.6, 137.8, 129.8, 129.3, 128.2, 127.2, 122.1, 119.7, 116.2, 110.1, 63.2, 53.3, 49.4, 35.2, 29.9, 29.7.

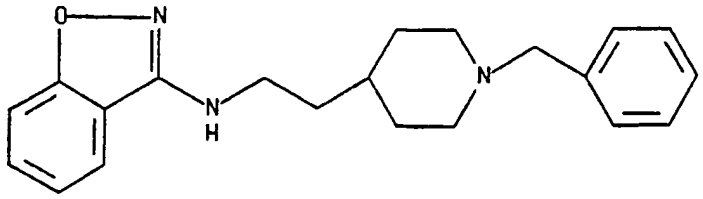
IR (KBr) 3290, 2924, 2852, 1614, 1564, 1450, 1365 cm^1.

EIMS: 321 (M+), 230, 201, 185, 172, 91 (base).

HRMS calc'd. for $C_{20}H_{23}N_3O$: 321.1842. Found: 321.1825.

Example 22

3-[2-[(1-Phenylmethyl)-4-piperidyl]ethylamino]-1,2-benzisoxazole



The procedure described in Example 21 was followed with 3-chloro-1,2-benzisoxazole (0.682 g, 4.44 mmol), 4-aminoethyl-1-phenylmethyl piperidine (0.970 g, 4.44 mmol), and K_2CO_3 (0.614 g, 4.44 mmol) in DMSO (30 mL). After purification, the title compound (0.231 g, 15%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 7.45-7.54 (m, 2H), 7.24-7.40 (m, 6H), 7.19 (t, 1H, J=7.8Hz), 4.40 (brt, 1H, J=5.5Hz), 3.52 (s, 2H), 3.45 (dt, 2H, J=7.4Hz, J=6.0Hz), 2.91 (brd, 2H, J=11.8Hz), 1.99 (brt, 2H, J=11.2Hz), 1.62-1.73 (m, 4H), 1.37-1.52 (m, 3H).

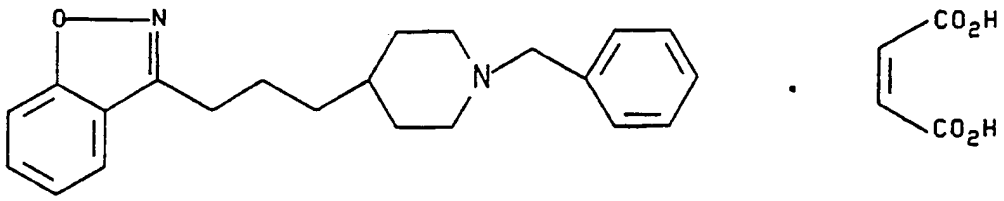
^{13}C-NMR ($CDCl_3$) δ 162.7, 158.6, 137.8, 129.8, 129.4, 128.2, 127.1, 122.1, 119.8, 116.3, 110.0, 63.3, 53.6, 41.5, 36.1, 33.4, 32.0.

EIMS: 335 (M+), 244, 199, 186, 172, 91 (base).

HRMS calc'd. for $C_{21}H_{25}N_3O$: 335.1998. Found: 335.1909.

Example 23

3-[3-[1-(Phenylmethyl)-4-piperidyl]propyl]-1,2-benzisoxazole maleate



a) 4-(2-Ethoxy-2-oxoethylidine)-1-piperidine-carboxylic acid, 1-(1,1-dimethylethyl)ester

A solution of triethyl phosphonoacetate (3.1 mL, 15.69 mmol) in freshly distilled 1,2-dimethoxyethane (DME, 12.5

mL) was added to a slurry of NaH (60% mineral oil dispersion, 0.75 g, 18.18 mmol) in DME (6.5 mL). The mixture obtained was stirred for 1 hour at room temperature and a solution of 4-keto-1-piperidinecarboxylic acid, 1-(1,1-dimethyethyl)ester (2.5 g, 12.55 mmol) in DME (12.5 mL) was added. After stirring overnight (15 hours), the mixture was concentrated. The residue was purified by silica gel flash chromatography (5→20% EtOAc-hexanes) to give the title compound (3.06 g, 91%) as a white solid.

^{1}H-NMR ($CDCl_3$) δ 5.71 (s, 1H), 4.16 (q, 2H, J=7.1Hz), 3.45-3.53 (m, 4H), 2.94 (t, 2H, J=5.7Hz), 2.28 (t, 2H, J=5.6Hz), 1.48 (s, 9H), 1.28 (t, 3H, J=7.1Hz).

b) 4-Ethoxycarbonylmethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

A mixture of olefin obtained in step a (3.05 g, 11.3 mmol) and 10% Pd/C (1.2 g, 1.13 mmol) in EtOH (50 mL) was hydrogenated in a Parr shaker at 50 psi for 1.5 hours. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give the title compound (3.07 g, quantitative) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 4.14 (q, 2H, J=7.0Hz), 4.05-4.12 (m, 2H), 2.72 (br dt, 2H, J=12.1Hz, J=2.8Hz), 2.23 (d, 2H, J=7.2Hz), 1.85-1.95 (m, 1H), 1.61-1.66 (m, 2H), 1.45 (s, 9H), 1.26 (t, 3H, J=7.0Hz), 1.05-1.23 (m, 2H).

c) 4-Hydroxyethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

The procedure described in Example 1b was followed with the ester obtained in step b (3.06 g, 11.3 mmol) and lithium aluminum hydride (0.47 g, 12.4 mmol) in THF (105 mL). Purification by silica gel flash chromatography (50% EtOAc-hexanes) gave unreacted starting material (0.73 g, 24%) and the title compound (1.74 g, 68%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) 4.07 (br d, 2H, J=14.1Hz), 3.71 (t, 2H, J=6.5Hz), 2.69 (brt, 2H, J=12.5Hz), 1.50-1.70 (m, 6H), 1.45 (s, 9H), 1.05-1.15 (m, 2H).

d) 4-Iodoethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

The procedure described in Example 1c was followed with the alcohol obtained in step c (1.74 g, 7.59 mmol), triphenylphosphine (2.49 g, 9.49 mmol), iodine (2.31 g, 9.11 mmol), and pyridine (1.5 mL, 18.2 mmol) in benzene (50 mL). After purification, the title compound (2.27 g, 98%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 4.09 (br d, 2H, J=11.4Hz), 3.22 (t, 2H, J=7.3Hz), 2.70 (brt, 2H, J=12.5Hz), 1.78 (q, 2H, J=6.9Hz), 1.47-1.68 (m, 3H), 1.46 (s, 9H), 1.12 (ddd, 2H, J=24.3Hz), J=12.9Hz, J=4.3Hz).

e) 4-[3-[1,2-Benzisoxazol-3-yl]propyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

The procedure described in Example 1d was followed with 3-methyl-1,2-benzisoxazole (0.412 g, 3.09 mmol), the iodide obtained in step d (1.15 g, 3.4 mmol), and 1M LDA (3.4 mL, 3.4 mmol) in THF (8 mL). After purification, the title compound (0.694 g, 65%) was obtained as pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 7.65 (d, 1H, J=8.0Hz), 7.54-7.57 (m, 2H), 7.27-7.34 (m, 1H), 4.08 (brd, 2H, J=12.5Hz), 2.99 (t, 2H, J=7.6Hz), 2.66 (brt, 2H, J=12.0Hz), 1.86-1.92 (m, 2H), 1.63-1.68 (m, 4H), 1.45 (s, 9H), 1.36-1.45 (m, 1H), 1.06-1.12 (m, 2H).

f) 3-[3-[1-(Phenylmethyl)-4-piperidyl]propyl]-1,2-benzisoxazole maleate

The procedure described in Example 1e was followed with piperidine obtained in step e (0.544 g, 1.58 mmol) and TFA (4 mL) in CH_2Cl_2 (16 mL), and triethylamine (1.1 mL, 7.9 mmol) and benzyl bromide (0.21 mL, 1.74 mmol) in CH_2Cl_2 (10 mL) for 7.25 hours. Purification by chromatography (2→5% MeOH-CH_2Cl_2) gave the title compound, free base (0.285 g, 54%) as a pale yellow oil.

The maleate salt was prepared by adding maleic acid (0.109 g, 0.94 mmol) dissolved in the minimum amount of EtOH to a solution of the free base (0.285 g, 0.85 mmol) in CH_2Cl_2 (10 mL). After concentrating, the residue was purified by

recrystallization (EtOAc) to give the title compound (0.292 g, 76%) as an off-white solid.

M.p.: 134.5-135.5.

^{1}H-NMR (DMSO-d_6) δ 7.90 (d, 1H, J=7.9Hz), 7.61-7.72 (m, 2H), 7.47 (s, 5H), 7.38 (t, 1H, J=7.3Hz), 6.04 (s, 2H), 4.26 (br s, 2H), 3.22-3.45 (m, 2H), 2.99 (t, 2H, J=7.4Hz), 2.70-2.96 (m, 2H), 1.70-1.90 (m, 4H), 1.40-1.65 (m, 1H), 1.20-1.40 (m, 4H).

^{13}C-NMR (DMSO-d_6) δ 167.2, 162.2, 158.4, 135.8, 131.2, 130.3, 129.5, 128.9, 123.5, 122.1, 121.2, 109.7, 59.3, 51.7, 34.8, 32.6, 28.9, 24.5, 24.1.

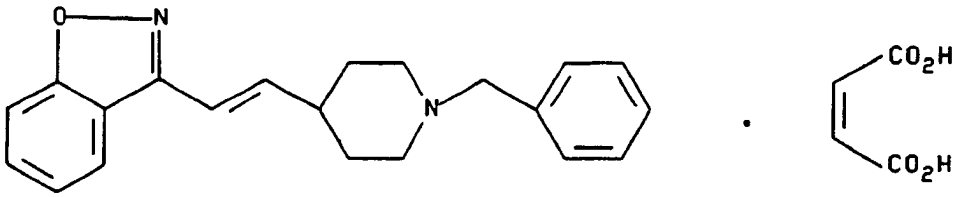
IR (KBr) 2942, 1705, 1581, 1460, 1359 cm^{-1}.

EIMS: 334 (M+, free base), 243, 202, 173 (base), 91.

Anal. calc'd. for $C_{22}H_{26}N_2O \cdot C_4H_4O_4$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.11; H, 6.64; N, 6.46.

Example 24

trans-3-[2-[1-(Phenylmethyl)-4-piperidyl]-1,2-benzisoxazole maleate



NaH (60% mineral oil dispersion, 0.10 g, 2.51 mmol) was added to a mixture of 3-triphenylphosphoniummethyl-1,2-benzisoxazole bromide (1.19 g, 2.51 mmol) in THF (10 mL). After stirring at room temperature for 1 hour, a solution of 4-carboxaldehyde-1-phenylmethylpiperidine (0.51 g, 2.51 mmol) in THF (2 mL) was added. The mixture obtained was stirred for 4 hours and filtered. The filtrate was concentrated and the residue was partitioned between diethyl ether and H_2O. The separated organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (40% EtOAc-hexanes) gave the title compound, free base (0.483 g, 60%) as a colorless oil.

The maleate salt was prepared by adding maleic acid (0.194 g, 1.67 mmol) dissolved in the minimum amount of EtOH to a solution of the free base (0.483 g, 1.52 mmol) in Et_2O (25 mL). The white solid obtained was collected by filtration to give the title compound (0.581 g, 88%).

M.p.: 174-175°C.

^{1}H-NMR (DMSO-d_6) δ 8.16 (d, 1H, J=7.8Hz), 7.75 (d, 1H, J=8.4Hz), 7.67 (t, 1H, J=8.2Hz), 7.41-7.55 (m, 6H), 6.96 (br dd, 1H, J=16.5Hz, J=5.6Hz), 6.78 (d, 1H, J=16.5Hz), 6.08 (s, 2H), 4.33 (s, 2H), 3.32-3.39 (m, 2H), 2.95-3.15 (m, 2H), 2.50-2.70 (m, 1H), 2.06 (br d, 2H, J=12.6Hz), 1.60-1.90 (m, 2H).

^{13}C-NMR (DMSO-d_6) δ 167.3, 162.7, 154.9, 142.7, 135.9, 131.2, 130.4, 130.2, 129.5, 128.9, 124.2, 122.7, 119.4, 116.5, 109.9, 59.2, 51.0, 36.2, 27.8.

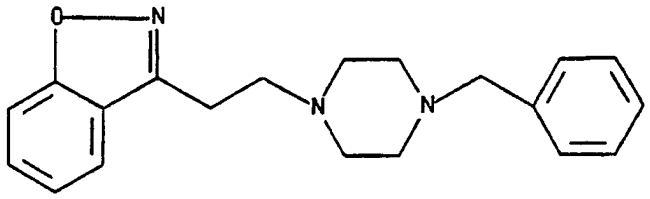
IR (KBr) 3035, 2944, 1708, 1588, 1472, 1360 cm^{-1}.

EIMS: 3.18 (M+, free base), 201, 227, 172, 91 (base).

Anal. Calc'd. for $C_{21}H_{22}N_2O \cdot C_4H_4O_4$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.04; H, 6.27; N, 6.38.

Example 25

3-[2-[1-(Phenylmethyl)-4-piperazinyl]ethyl]-1,2-benzisoxazole dihydrochloride salt



· 2HCl

A mixture of 3-(2-chloroethyl)-1,2-benzisoxazole (0.55 g, 3.03 mmol) and N-benzylpiperazine (1.06 mL, 6.06 mmol) in xylene (4 mL) was heated at 150°C for 4.75 hours. The cooled mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification by silica gel flash chromatography (50% EtOAc-hexanes→100% EtOAc) gave the title compound, free base (0.337 g, 35%) as a pale yellow oil.

The dihydrochloride salt was made by bubbling excess hydrogen chloride through a solution of the free base (0.337

g, 1.05 mmol) in Et_2O (50 mL). The white solid formed was collected by filtration to give the title compound (0.259 g, 63%).

M.p.: 233-234°C.

^{1}H-NMR (D_2O) δ 7.79 (d, 1H, J=8.0Hz), 7.53-7.69 (m, 2H), 7.50 (s, 5H), 7.40 (ddd, 1H, J=7.9Hz, J=6.6Hz, J=1.3Hz), 4.47 (s, 2H), 3.82 (t, 2H, J=7.5Hz), 3.60-3.80 (m, 8H), 3.55 (t, 2H, J=7.5Hz).

^{13}C-NMR (D_2O) δ 165.5, 158.0, 134.1, 133.6, 132.4, 130.3, 127.1, 124.4, 123.2, 112.8, 63.4, 56.6, 51.8, 51.0, 23.2.

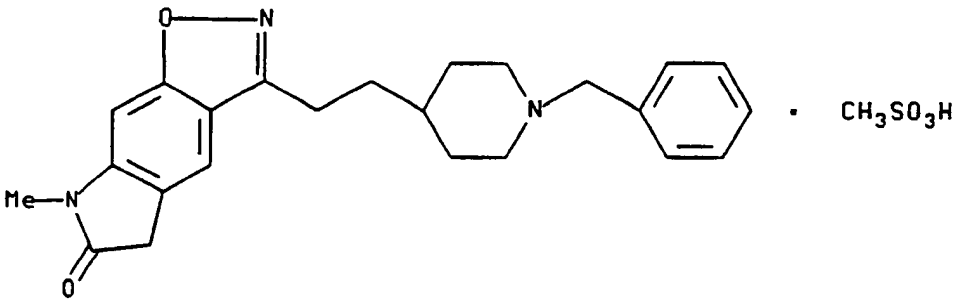
IR (KBr) 2989, 1608, 1436, 1375 cm^{-1}.

EIMS: 321 (M+, free base), 256, 189, 91 (base).

Anal. Calc'd. for $C_{20}H_{23}N_3O \cdot 2HCl$: C, 60.92; H, 6.39; N, 10.66. Found: C, 60.64; H, 6.57; N, 10.42.

Example 26

5,7-Dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazole-6-one mesylate



NaH (60% mineral oil dispersion, 0.048 g, 1.2 mmol) was added to a solution of 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazole-6-one (0.374 g, 1.0 mmol) in DMF (10 mL) at room temperature. After evolution of hydrogen gas had subsided, methyl iodide (0.093 mL, 1.5 mmol) was added and the mixture obtained was stirred for 5.5 hours. Saturated NH_4Cl and H_2O (>50 mL) were added. The reaction was extracted with CH_2Cl_2 and the organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography ($CH_2Cl_2 \rightarrow 3\%$

MeOH-CH_2Cl_2) gave the title compound, free base (0.056 g, 14%) as an off-white foam.

The mesylate salt was made by adding methanesulfonic acid (0.009 mL, 0.144 mmol) to a solution of the free base (0.056 g, 0.044 mmol) in CH_2Cl_2 (5 mL). After concentration, the residue was triturated from Et_2O to give the title compound (0.049 g, 70%) as an off-white solid.

M.p.: 164-165°C (dec).

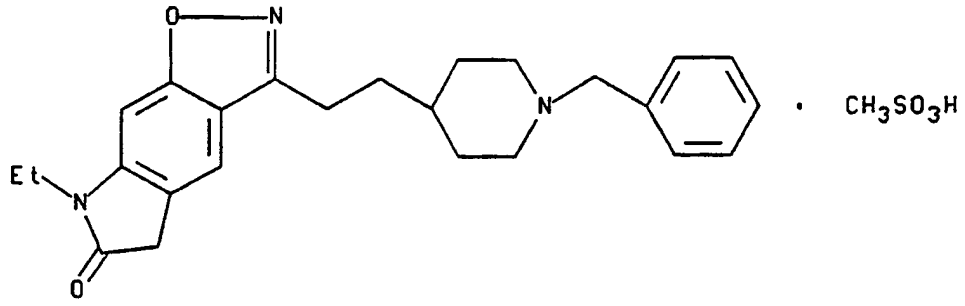
^{1}H-NMR (DMSO-d_6) 7.69 (s, 1H), 7.49 (s, 5H), 7.32 (s, 1H), 4.28 (s, 2H), 3.64 (s, 2H), 3.35 (br d, 2H, J=11.6Hz), 3.18 (s, 3H), 2.85-2.99 (m, 4H), 2.30 (s, 3H), 1.95 (br d, 2H, J=12.9Hz), 1.66-1.80 (m, 2H), 1.45-1.60 (m, 1H), 1.35-1.44 (m, 2H).

EIMS: 389 (M+, free base), 298, 217, 200, 185 (base), 172.

HRMS Calc'd. for $C_{24}H_{27}N_3O_2 \bullet CH_3SO_3H$: 389.2104. Found: 389.2075.

Example 27

5,7-Dihydro-7-ethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one mesylate



The procedure described in Example 26 was followed with 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one (0.374 g, 1.0 mmol), NaH (0.068 g, 1.7 mmol), and ethyl iodide (0.16 mL, 2.0 mmol) in DMF (10 mL). After purification, the title compound, free base (0.076 g, 19%) was obtained as a pale yellow oil.

The mesylate salt was made by adding methanesulfonic acid (0.007 mL, 0.112 mmol) to a solution of the free base (0.045 g, 0.112 mmol) in CH_2Cl_2 (5 mL). After concentration, the residue was triturated from Et_2O to give the title compound (0.042 g, 75%) as an off-white solid (hygroscopic).

M.p.: ~162°C (dec at >60°C)

^{1}H-NMR (DMSO-d_6) δ 7.69 (s, 1H), 7.48 (s, 5H), 7.39 (s, 1H), 4.27 (s, 2H), 3.77 (br q, 2H, J=7.1Hz), 3.64 (s, 2H), 3.34-3.39 (m, 2H), 2.92-2.98 (m, 4H), 2.30 (s, 3H), 1.94 (br d, 2H, J=12.8Hz), 1.66-1.78 (m, 2H), 1.30-1.60 (m, 3H), 1.16 (t, 3H, J=7.1Hz).

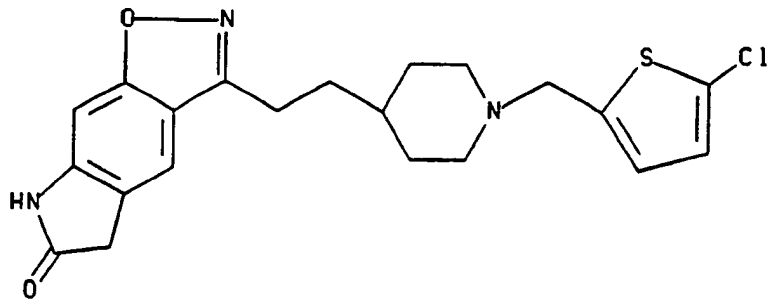
^{13}C-NMR (DMSO-d_6) 174.5, 163.2, 158.1, 147.0, 131.4, 131.0, 129.8, 129.6, 128.9, 121.2, 117.0, 115.2, 90.0, 59.3, 51.6, 34.5, 34.4, 33.0, 32.6, 28.5, 21.6, 12.3.

IR (KBr) 2934, 1716, 1630, 1605, 1466, 1330 cm^{-1}.

EIMS 403 (M+, free base), 386, 312, 185 (base), 172.

HRMS Calc'd. for $C_{25}H_{29}N_3O_2 \bullet CH_3SO_3H$: 403.22605. Found: 403.22761.

Example 28



5,7-Dihydro-3-[2-[1-(2-chloro-5-thiophenemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one

The procedure described in Example 12f was followed with4-[2-[5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (0.328 g, 0.851 mmol) and TFA (2 mL) in CH_2Cl_2 (8 mL). Only a portion of the crude salt was utilized in the alkylation step: Na_2CO_3 (0.175 g, 1.66 mmol) and 2-chloro-5-chloromethylthiophene (0.048 mL, 0.40 mmol) in DMF

(3 mL). After purification (2-4% MeOH-CH_2Cl_2), the title compound (0.0514 g, 43%) was obtained as a white solid.

M.p.: 202-204°C (dec)

^{1}H-NMR (DMSO-d_6) δ 10.8 (s, 1H), 7.62 (s, 1H), 6.97 (s, 1H), 6.92 (d, 1H, J=3.7Hz), 6.80 (d, 1H, J=3.7Hz), 3.57 (s, 2H), 3.55 (s, 2H), 2.81-2.93 (m, 4H), 1.91 (br t, 2H, J=10.7Hz), 1.61-1.71 (m, 4H), 1.11-1.23 (m, 3H).

^{13}C-NMR (DMSO-d_6) δ 176.7, 162.9, 158.3, 146.5, 142.8, 127.0, 126.1, 125.1, 123.2, 117.1, 115.1, 90.1, 57.0, 53.0, 35.0, 34.8, 33.9, 31.6, 21.9.

IR (KBr) 3174, 2950, 1702, 1631, 1453, 1330 cm^{-1}.

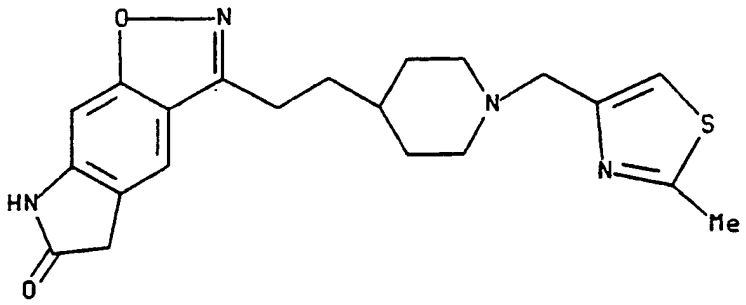
EIMS: 398, 382, 350, 322, 236, 172, 91, 81 (base).

HRMS calc'd. for $C_{21}H_{22}ClN_3O_2S$: 415.1122. Found: 415.1085.

Anal. Calc'd. for $C_{21}H_{22}ClN_3O_2S \cdot 0.5H_2O$: C, 59.36; H, 5.46; N, 9.89. Found: C, 59.21; H, 5.12; N, 9.65.

Example 29

5,7-Dihydro-3-[2-[1-(2-methyl-4-thiazolemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one



The procedure described in Example 12f was followed with 4-[2-[5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (0.367 g, 0.952 mmol) and TFA (2.5 mL) in CH_2Cl_2 (10 mL), and Na_2CO_3 (1.01 g, 9.52 mmol) and 4-chloromethyl-2-methylthiazole hydrochloride salt (0.210 g, 1.142 mmol) in DMF (10 mL). Purification by chromatography (4% MeOH-EtOAc) followed by recrystallization (EtOAc-hexanes) gave the title compound (0.074 g, 20%) as a white solid.

M.p.: 172-173°C (dec.)

^{1}H-NMR ($CDCl_3$) δ 9.40 (br s, 1H), 7.41 (s, 1H), 7.05 (s, 1H), 7.02 (s, 1H), 3.72 (s, 2H), 3.61 (s, 2H), 3.07 (brd, 2H, J=11.3Hz), 2.93 (t, 2H, J=7.8Hz), 2.69 (s, 3H), 2.15 (brt, 2H, J=10.8Hz), 1.76-1.85 (m, 4H), 1.42-1.55 (m, 3H).

^{13}C-NMR ($CDCl_3$) δ 177.4, 166.0, 163.6, 158.3, 151.7, 145.1, 122.2, 116.9, 116.8, 116.3, 91.5, 57.8, 53.4, 35.4, 34.8, 34.0, 31.2, 22.5, 19.2.

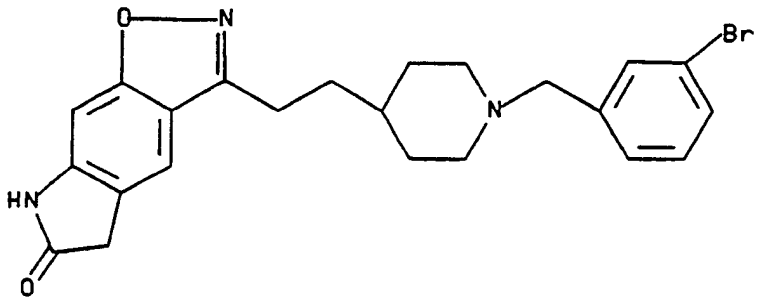
IR (KBr) 3101, 3015, 2938, 2924, 1713, 1633, 1456, 1328 cm^{-1}.

EIMS: 396 (M+), 379, 284, 267, 206 (base).

HRMS calc'd. for $C_{21}H_{24}N_4O_2S$: 396.1621. Found: 396.1631.

Example 30

3-[2-[1-(3-Bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H pyrrolo[4,5-f]-1,2-benzisoxazol-6-one



The procedure described in Example 12f was followed with 4-[2-[5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (0.50 g, 1.30 mmol) and TFA (3 mL) in Ch_2Cl_2 (12 mL), and Na_2CO_3 (0.689 g, 6.5 mmol) and 3-bromobenzyl bromide (0.46g, 1.84 mmol) in DMF (20 mL). Purification aby chromatography (CH_2Cl_2 → 5% MeOH-CH_2Cl_2) gave the title compound (0.314 g, 53%) as a pale yellow solid. Recrystallization (EtOAc, twice) gave a white solid (0.076 g, 13%).

M.p.: 173-174°C.

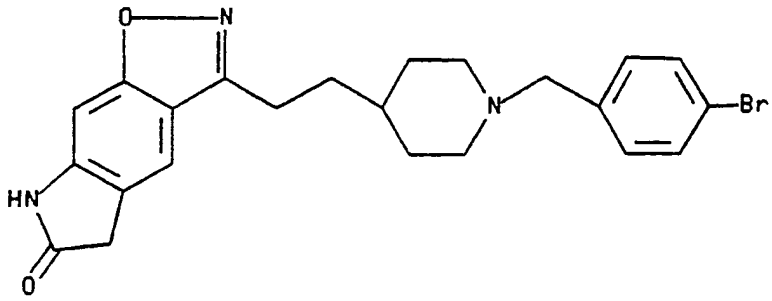
^{1}H-NMR ($CDCl_3$) δ 8.77 (s, 1H), 7.47 (s, 1H), 7.41 (s, 1H), 7.36 (d, 1H, J=7.7Hz), 7.23 (d, 1H, J=7.9Hz), 7.16 (t,

1H, J=7.7Hz), 7.00 (s, 1H), 3.61 (s, 2H), 3.46 (s, 2H), 2.86-2.96 (m, 4H), 1.90-2.02 (m, 2H), 1.70-1.85 (m, 4H), 1.30-1.42 (m, 3H).

^{13}C-NMR ($CDCl_3$) δ 177.1, 163.5, 158.4, 144.7, 132.0, 130.1, 129.8, 127.8, 122.3, 122.0, 116.9, 116.5, 91.5, 62.6, 53.6, 35.3, 35.2, 34.3, 31.9, 22.6.

Example 31

3-[2-[1-(4-Bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one



The procedure described in Example 12f was followed with 4-[2-[5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethyl-ethyl)ester (0.50 g, 1.3 mmol) and TFA (3 mL) in CH_2Cl_2 (12 mL), and Na_2CO_3 (0.689 g, 6.5 mmol) and 4-bromobenzyl bromide (0.39 g, 1.56 mmol) in DMF (15 mL). Purification by chromatography (CH_2Cl_2 → 5% MeOH-CH_2Cl_2) gave the title compound (0.415 g, 70%) as an off-white solid.

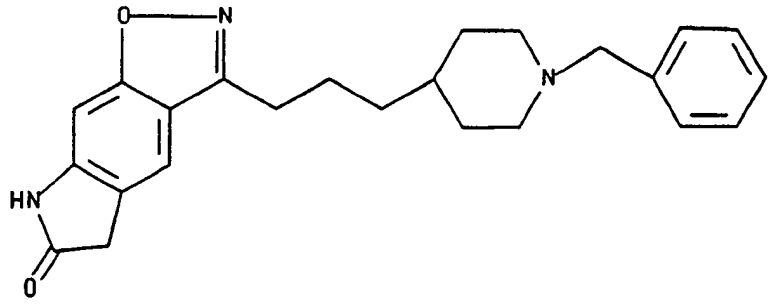
M.p.: 177-178°C.

^{1}H-NMR ($CDCl_3$) δ 9.98 (br s, 1H), 7.37-7.40 (m, 3H), 7.16 (d, 2H, J=8.2Hz), 6.99 (s, 1H), 3.60 (s, 2H), 3.42 (s, 2H), 2.87-2.94 (m, 4H), 1.94 (brt, 2H, J=10.5Hz), 1.65-1.80 (m, 4H), 1.20-1.35 (m, 3H).

^{13}C-NMR ($CDCl_3$) δ 178.1, 163.5, 158.4, 145.2, 137.3, 131.2, 130.8, 122.2, 120.7, 116.7, 116.3, 91.5, 62.5, 53.5, 35.5, 35.2, 34.2, 31.9, 22.5.

Example 32

5,7-Dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]-propyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one



a) 4-[3-[5,7-Dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one-3-yl]propyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

The procedure described in Example 7a was followed with 5,7-dihydro-3-methyl-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one (0.13 g, 0.69 mmol), 1M LDA (2.8 mL, 2.8 mmol), and 4-iodoethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (0.233 g, 0.69 mmol) in dry THF (14 mL), except that after addition of reagents, the mixture was stirred at -78°C for 4 hours. Purification by chromatography (10% → 50% EtOAc-CH_2Cl_2) gave recovered starting material (0.031 g, 24%) and the title compound (0.129 g, 47%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 9.50 (s, 1H), 7.42 (s, 1H), 7.04 (s, 1H), 4.06 (brd, 2H, J=14.5Hz), 3.62 (s, 2H), 2.91 (t, 2H, J=7.5Hz), 2.66 (dt, 2H, J=13.0Hz, J=2.0Hz), 1.81-187 (m, 2H), 1.65 (brd, 2H, J=12.3Hz), 1.44 (s, 9H), 1.34-1.43 (m, 3H), 1.09-1.20 (m, 2H).

b) 5,7-Dihydro-3-[3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one

The procedure described in Example 12f was followed with the piperidine obtained in step a (0.114 g, 0.29 mmol) and TFA (1.5 mL) in CH_2Cl_2 (6 mL), and Na_2CO_3 (0.154 g, 1.45 mmol) and benzyl bromide (0.042 mL, 0.35 mmol) in DMF (5 mL). Purification by chromatography (CH_2Cl_2 → 5% MeOH-CH_2Cl_2) gave the title compound (0.070 g, 62%) as a white foamy

solid. Recrystallization (CH_2Cl_2) gave a white solid (0.054 g, 48%).

M.p.: 164-166°C.

^{1}H-NMR ($CDCl_3$) δ 9.73 (br s, 1H), 7.41 (s, 1H), 7.24-7.34 (m, 5H), 6.99 (s, 1H), 3.61 (s, 2H), 3.56 (s, 2H), 2.86-2.97 (m, 4H), 1.97-2.05 (m, 2H), 1.76-1.88 (m, 2H), 1.65-1.70 (m, 2H), 1.26-1.38 (m, 5H).

^{13}C-NMR ($CDCl_3$) 177.7, 163.6, 158.3, 145.2, 129.5, 128.3, 127.3, 122.2, 116.8, 116.4, 91.6, 63.2, 53.6, 36.1, 35.5, 35.3, 31.9, 25.4, 25.0.

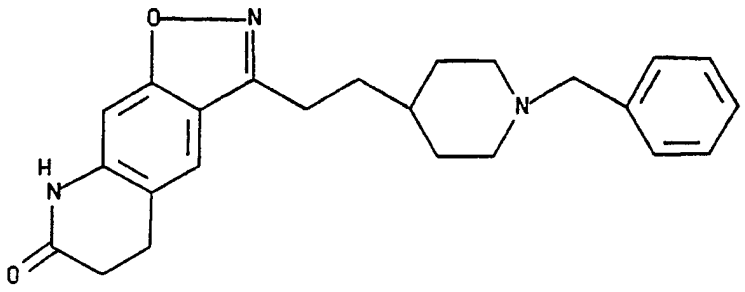
IR (KBr) 3150, 3096, 2930, 1705, 1634, 1495, 1345 cm^{-1}.

EIMS 389 (M+), 372, 298, 202, 172, 108, 91 (base).

HRMS calc'd. for $C_{24}H_{27}N_3O$: 389.2104. Found: 389.2107.

Example 33

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-5,6,8-trihydro-7H-isoxazolo[4,5-g]quinolin-7-one



a) 6-Acetyl-3,4-dihydro-7-hydroxy-2H-quinolin-2-one

Acetyl chloride (2.0 mL, 28.1 mmoL) was added to a mixture of 3,4-dihydro-7-methoxy-2H-quinolin-2-one (1.99 g, 11.2 mmol) in 1,2-dichloroethane (30 mL). The mixture obtained was cooled to 0°C and $AlCl_3$ (6.0 g, 44.98 mmol) was added in portions. The mixture was heated to reflux for 2 hours. The reaction was cautiously poured over ice-H_2O, stirred for a minimum of 1 hour (to overnight), and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the title compound (1.89 g, 82%) as an off-white solid.

^{1}H-NMR (DMSO-d_6) δ 12.4 (s, 1H), 10.4 (s, 1H), 7.74 (s, 1H), 6.38 (s, 1H), 2.86 (t, 2H, J=7.4Hz), 2.56 (s, 3H), 2.46-2.56 (m, 2H).

b) 6-Acetyl-3,4-dihydro-7-hydroxy-2H-quinolin-2-one, 6-oxime

An aqueous solution of hydroxylamine hydrochloride (1.47 g, 21.2 mmol) and sodium acetate trihydrate (3.0 g, 22.1 mmoL) was added to a mixture of the ketone obtained in step a (1.89 g, 9.2 mmol) in EtOH (100 mL). The mixture obtained was heated to reflux for 4 hours. The reaction was concentrated, and the residue was stirred with H_2O. The solid obtained was collected by filtration, and rinsed with EtOH and Et_2O to give the title compound (1.67 g, 82%) as an off-white solid.

M.p.: 286.5-287.7°C (dec).

^{1}H-NMR (DMSO-d_6) δ 11.7 (s, 1H), 11.3 (s, 1H), 10.1 (s, 1H), 7.28 (s, 1H), 6.37 (s, 1H), 2.81 (t, 2H, J=7.5Hz), 2.43 (t, 2H, J=7.5Hz), 2.21 (s, 3H).

c) 6-Acetyl-3,4-dihydro-7-hydroxy-2H-quinolin-2-one, 6-oxime acetate

A heterogenous mixture of the oxime obtained in step b (1.67 g, 7.57 mmol) in acetic anhydride (13 mL) was heated at 80°C for 1.5 hours. The reaction mixture was concentrated, and excess acetic anhydride was removed by concentrating from toluene. After drying, the title compound (1.7 g, 86%) was obtained as an off-white solid.

^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H), 10.2 (s, 1H), 7.36 (s, 1H), 6.44 (s, 1H), 2.82 (t, 2H, J=7.5Hz), 2.45 (t, 2H, J=7.5Hz), 2.38 (s, 3H), 2.22 (s, 3H).

d) 5,6,8-Trihydro-7H-isoxazolo[4,5-g]quinolin-7-one

A mixture of the oxime acetate obtained in step c (1.58 g, 6.02 mmol) and pyridine (4.9 mL, 60.2 mmol) in DMF (75 mL) was heated in 125-130°C for 2 hours. The reaction was concentrated in vacuo and the residue obtained was purified by recrystallization (EtOAc) to give the title compound (0.80 g, 66%) as a pale yellow solid.

M.p.: 309-311°C (dec).

^{1}H-NMR (DMSO-d_6) δ 10.4 (s, 1H), 7.62 (s, 1H), 7.02 (s, 1H), 2.99 (t, 2H, J=7.4Hz), 2.49-2.53 (m, 2H), 2.47 (s, 3H).

e) 4-[2-[5,6,8-Trihydro-7H-isoxazolo[4,5-g]quinolin-7-one-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

The procedure described in Example 7a was followed with the benzisoxazole obtained in step d (0.47 g, 2.3 mmol), 1M LDA (8.1 mL, 8.1 mmol), and 4-iodomethyl-1-piperidine-carboxylic acid, 1-(1,1-dimethylethyl)ester (0.75 g, 2.3 mmol) in dry THF (150 mL), except that after addition of reagents, the mixture was stirred at -78°C for 3.5 hours. An additional reaction was benzisoxazole obtained in step d (0.206 g, 1.02 mmol) was carried out in the same manner. Crude product from both reactions was combined and purification by chromatography (EtOAc) gave the title compound (0.72 g, 54% as a white solid.

^{1}H-NMR (DMSO-d_6) δ 10.4 (s, 1H), 7.67 (s, 1H), 7.02 (s, 1H), 3.93 (brd, 2H, J=13.4Hz), 2.89-3.31 (m, 4H), 2.57-2.75 (brm, 2H), 2.49-2.53 (m, 2H), 1.64-1.72 (m, 4H), 1.38 (s, 9H), 1.36-1.50 (m, 1H), 1.01-1.16 (m, 2H).

f) 3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-5,6,8-trihydro-7H-isoxazolo[4,5-g]quinolin-7-one

The procedure described in Example 12f was followed with the piperidine obtained in step e (0.55 g, 1.37 mmol) and TFA (3.5 mL) in CH_2Cl_2 (14 mL), and Na_2CO_3 (0.758 g, 7.14 mmol) and benzyl bromide (0.23 mL, 1.93 mmol) in DMF (14 mL). After purification by chromatography (5-30% MeOH-CH_2Cl_2), the title compound (0.23 g, 43%) was obtained as a white solid. A sample could be recrystallized from EtOAc-MeOH.

M.p.: 164.4-165.9°C.

^{1}H-NMR ($CDCl_3$) δ 9.37 (s, 1H), 7.38 (s, 1H), 7.22-7.36 (m, 5H), 7.01 (s, 1H), 3.55 (s, 2H), 3.09 (t, 2H, J=7.4Hz), 2.91-2.97 (m, 4H), 2.70 (t, 2H, J=7.4Hz), 2.01 (brt, 2H, J=10.3Hz), 1.75-1.80 (m, 4H), 1.39-1.50 (m, 3H).

^{13}C-NMR ($CDCl_3$) 170.6, 162.0, 158.2, 141.1, 140.9, 128.7, 128.2, 126.8, 121.2, 120.3, 115.7, 94.6, 62.5, 53.2, 34.9, 33.8, 31.6, 30.2, 24.8, 21.9.

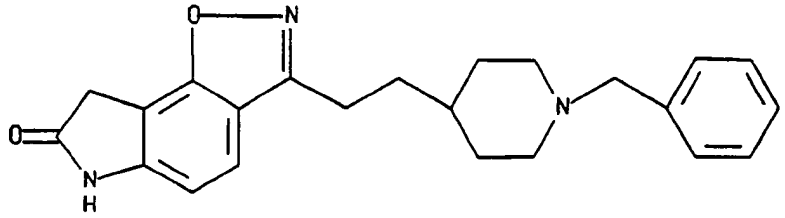
IR (KBr) 3172, 3088, 2921, 1694, 1631, 1447, 1381 cm^{-1}.

EIMS 389 (M+), 388, 372, 298, 185, 172, 91 (base).

HRMS Calc'd. for $C_{24}H_{27}N_3O_2$: 389.2104. Found: 389.2102.

Example 34

6,8-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one



a) 5-Acetyl-1,3-dihydro-4-hydroxy-2H-indol-2-one

An intimate mixture of 4-acetyloxy-1,3-dihydro-2H-indol-2-one (0.876 g, 4.58 mmol) and $AlCl_3$ (1.83 g, 13.7 mmol) placed in a tear-shape flask was immersed in an oil bath pre-heated to 190°C and heated for 1 hour. Ice-water was added cautiously to the cooled reaction mixture and stirred for 1.5 hours. Concentrated HCl was added and the mixture was extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (1 → 3% MeOH-CH_2Cl_2) gave the title compound (0.441 g, 50%) as an off-white solid.

^{1}H-NMR (DMSO-d_6) δ 12.6 (s, 1H), 10.8 (s, 1H), 7.85 (d, 1H, J=8.4Hz), 6.49 (d, 1H, J=8.4Hz), 3.41 (s, 2H), 2.57 (s, 3H).

b) 5-Acetyl-1,3-dihydro-4-hydroxy-2H-indol-2-one, 5-oxime

The procedure described in Example 33b was followed with the ketone obtained in step a (0.40 g, 2.09 mmol), and an aqueous solution of NH_2OH hydrochloride (0.29 g, 4.18 mmol), and NaOAc trihydrate (0.569 g, 4.18 mmol) in EtOH (32 mL). After 3 hours, the mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried ($MgSO_4$),

filtered, and concentrated to give the title compound (0.436 g, quantitative) as an off-white solid.

^{1}H-NMR (DMSO-d_6) δ 12.0 (s, 1H), 11.4 (s, 1H), 10.4 (s, 1H), 7.35 (d, 1H, J=8.2Hz), 6.41 9d, 1H, 8.3Hz), 3.34 (s, 2H), 2.22 (s, 3H).

c) 5-Acetyl-1,3-dihydro-4-hydroxy-2H-indol-2-one, 5-oxime acetate

The procedure described in Example 33c was followed with the oxime obtained in step b (0.392 g, 1.9 mmol) in Ac_2O (10 mL). The solid obtained was freed from any inorganic salts from previous step by stirring in H_2O. Filtration and drying gave the title compound (0.417 g, 88%) as a red-pinkish solid.

^{1}H-NMR (DMSO-d_6) δ 11.45 (s, 1H), 10.6 (s, 1H), 7.50 (d, 1H, J=8.2Hz), 6.49 (d, 1H, J=8.2Hz), 3.40 (s, 2H), 2.41 (s, 3H), 2.23 (s, 3H).

d) 6,8-Dihydro-3-methyl-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one

The procedure described in Example 33d was followed with the oxime acetate obtained in step c (0.334 g, 1.35 mmol) and pyridine (0.55 mL, 6.75 mmol) in DMF (25 mL). After work-up, the residue was purified by silica gel flash chromatography (50 → 75% EtOAc-hexanes) to give the title compound (0.086 g, 34%) as a white solid.

M.p.: 259-260°C (dec).

^{1}H-NMR (DMSO-d_6) δ 10.79 (s, 1H), 7.67 (d, 1H, J=8.5Hz), 6.92 (d, 1H, J=8.3Hz), 3.73 (s, 2H), 2.49 (s, 3H).

e) 4-[2-[6,8-Dihydro-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one-3-yl]ethyl]-1-piperidinecarboxylic acid 1-(1,1-dimethylethyl)ester

The procedure described in Example 7a was followed with the benzisoxazole obtained in step d (0.040 g, 0.213 mmol), 1M LDA (0.85 mL, 0.85 mmol), and 4-iodomethyl-1-piperidine-carboxylic acid, 1-(1,1-dimethylethyl)ester (0.078 g, 1.234 mmol) in dry THF (20 mL), except that after addition of reagents, the mixture was stirred at -78°C for 4 hours.

Purification by chromatography (25 → 45% EtOAc-CH_2Cl_2) gave the title compound (0.042 g, 51%) as a pale yellow solid.

^{1}-NMR ($CDCl_3$) δ 8.85 (s, 1H), 7.53 (d, 1H, J=8.1Hz), 6.95 (d, 1H, J=8.3Hz), 4.08-4.14 (m, 2H), 3.78 (s, 2H), 2.99 (t, 2H, J=7.8Hz), 2.68 (brt, 2H, J=12.1Hz), 1.73-1.84 (m, 4H), 1.46-1.60 (m, 1H), 1.46 (s, 9H), 1.17 (ddd, 2H, J=23.2Hz, J=12.1Hz, J=4.3Hz).

f) 6,8-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one

The procedure described in Example 12f was followed with the piperidine obtained in step e (0.042 g, 0.109 mmol) and TFA (1.5 mL) in CH_2Cl_2 (6 mL), Na_2CO_3 (0.058 g, 0.545 mmol) and benzyl bromide (0.016 mL, 0.131 mmol) in DMF (6 mL). After purification by chromatography (1-10% MeOH-CH_2Cl_2), the title compound (0.018 g, 44%) was obtained as an off-white solid.

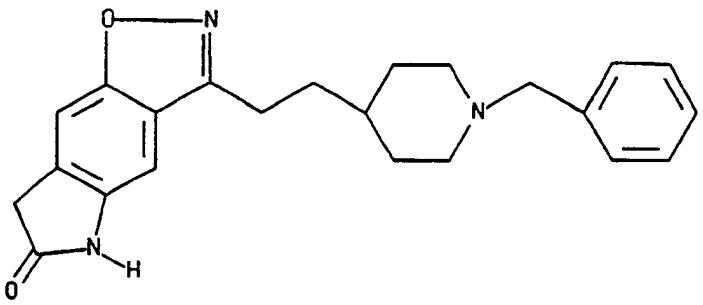
M.p.: 188-189°C.

^{1}H-NMR ($CDCl_3$) δ 9.59 (s, 1H), 7.51 (d, 1H, J=8.1Hz), 7.23-7.33 (m, 5H), 6.94 (d, 1H, J=8.2Hz), 3.77 (s, 2H), 3.56 (s, 2H), 2.93-2.99 (m, 4H), 2.02 (brt, 2H, J=10.7Hz), 1.75-1.79 (m, 4H), 1.26-1.39 (m, 3H).

^{13}C-NMR ($CDCl_3$) δ 177.2, 158.9, 158.5, 145.0, 129.4, 128.3, 127.2, 121.5, 117.9, 107.1, 105.1, 63.2, 53.5, 35.1, 34.1, 33.8, 31.7, 29.7, 22.5.

Example 35

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-6H-pyrrolo[5,4-f]-1,2-benzisoxazol-6-one



a) 6-Acetyl-1,3-dihydro-5-hydroxy-2H-indol-2-one

The procedure described in Example 33a was followed with 1,3-dihydro-5-methoxy-2H-indol-2-one (4.4 g, 26.96 mmol), acetyl chloride (4.8 mL, 67.41 mmol), and $AlCl_3$ (14.4 g, 107.8 mmol) in 1,2-dichloroethane (210 mL) for 6 hours. After aqueous work-up and overnight stirring, a precipitate was obtained. This yellow solid was collected by filtration and dried to give the title compound (2.7 g, 52%).

^{1}H-NMR (DMSO-d_6) δ 12.0 (s, 1H), 10.4 (s, 1H), 7.12 (s, 1H), 6.89 (s, 1H), 3.54 (s, 2H), 2.61 (s, 3H).

b) 6-Acetyl-1,3-dihydro-5-hydroxy-2H-indol-2-one, 6-oxime

The procedure described in Example 33b was followed with the ketone obtained in step a (2.7 g, 14.4 mmol), and an aqueous solution of NH_2OH hydrochloride (2.26 g, 32.5 mmol) and NaOAc trihydrate (4.6 g, 33.9 mmol) in EtOH (155 mL) to give the title compound (2.7 g, 93%) as an off-white solid.

^{1}H-NMR (DMSO-d_6) δ 11.5 (s, 1H), 11.3 (s, 1H), 10.2 (s, 1H), 6.81 (s, 1H), 6.78 (s, 1H), 3.44 (s, 2H), 2.22 (s, 3H).

c) 6-Acetyl-1,3-dihydro-5-hydroxy-2H-indol-2-one, 6-oxime acetate

The procedure described in Example 33c was followed with the oxime obtained in step b (2.7 g, 13.1 mmol) in Ac_2O (65 mL) for 3 hours to give the title compound (2.93 g, 90%) as an off-white solid.

^{1}H-NMR (DMSO-d_6) δ 10.4 (s, 1H), 10.2 (s, 1H), 6.86 (s, 1H), 6.81 (s, 1H), 3.48 (s, 2H), 2.37 (s, 3H), 2.22 (s, 3H).

d) 5,7-Dihydro-3-methyl-6H-pyrrolo[5,4-f]-1,2-benzisoxazol-6-one

The procedure described in Example 33d was followed with the oxime acetate obtained in step c (2.75 g, 10.97 mmol) and pyridine (8.9 mL, 109.7 mmol) in DMF (110 m). After concentration in vacuo, the residue was purified by silica gel flash chromatography (2% MeOH-CH_2Cl_2) to give the title compound (0.245 g, 12%) as a pastel yellow solid.

^{1}H-NMR (DMSO-d_6) δ 10.6 (s, 1H), 7.58 (s, 1H), 7.03 (s, 1H), 3.63 (s, 2H), 2.50 (s, 3H).

e) 4-[2-[5,7-Dihydro-6H-pyrrolo[5,4-f]-1,2-benzisoxazol-6-one-3-yl]ethyl]-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester

The procedure described in Example 7a was followed with the benzisoxazole obtained in step d (0.152 g, 0.808 mmol), 1M LDA (3.2 mL, 3.2 mmol), and 4-iodomethyl-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (0.315 g, 0.970 mmol) in dry THF (30 mL), except that after addition of reagents, the mixture was stirred at -78°C for 4.5 hours. Purification by chromatography (50% EtOAc-CH_2Cl_2) gave an inseparable mixture (0.153 g, 1.6:1) of starting material and the title compound, respectively, as a pale yellow soft solid. In a separate experiment, a better ratio (starting material/title compound → 1:3) was observed.

^{1}H-NMR ($CDCl_3$) δ 9.84 (s, 1H), 7.45 (s, 1H), 7.05 (s, 1H), 4.05-4.15 (m, 2H), 3.69 (s, 2H), 2.96 (t, 2H, J=7.8Hz), 2.68 (brt, 2H, J=11.8Hz), 1.72-1.82 (m, 4H), 1.45 (s, 9H), 1.43-1.53 (m, 1H), 1.15 (ddd, 2H, J=23.6Hz, J=12.1Hz, J=4.0Hz).

f) 5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-6H-pyrrolo[5,4-f]-1,2-benzisoxazol-6-one

The procedure described in Example 12f was followed with the mixture obtained in step a (0.153 g) and TFA (1.5 mL) in CH_2Cl_2 (6 mL). Only a portion of the crude salt mixture (0.081 g) was utilized in the alkylation step: Na_2CO_3 (0.041 g, 0.388 mmol) and benzyl bromide (0.012 mL, 0.101 mmol) in DMF (6 mL). Note: For the alkylation step, the solvent (DMF) was thoroughly degassed with Ar and work-up with saturated $NaHCO_3$ was omitted (brine was used instead). After purification (2-6% MeOH-CH_2Cl_2), the title compound (0.018 g, 60% based on percentage of desired starting material) was obtained as a light yellow solid.

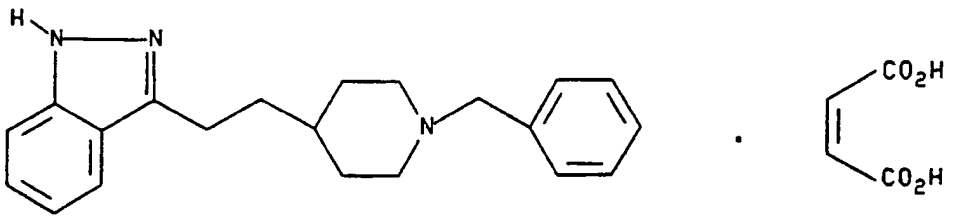
M.p.: 204.5-205.5°C (dec).

^{1}H-NMR ($CDCl_3$) δ 8.09 (s, 1H), 7.46 (s, 1H), 7.27-7.33 (m, 5H), 6.99 (s, 1H), 3.68 (s, 2H), 3.50-3.52 (m, 2H),

2.90-2.99 (m, 4H), 1.92-2.05 (m, 2H), 1.70-1.80 (m, 4H), 1.30-1.40 (m, 3H).

Example 36

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1H-indazole maleate



a) 1-(2-Fluorophenyl)-3-[1-(phenylmethyl)-4-piperidinyl]propanone

Lithium hexamethyldisilazide (1M, 14.5 mL, 14.5 mmol) was added to a solution of o-fluoroacetophenone (2.0 g, 14.5 mmol) in THF (100 mL) at -78°C. The mixture obtained was allowed to warm to -20°C over a 30-60 minute period and then re-cooled to -78°C. A solution of 4-carboxaldehyde-1-piperidinecarboxylic acid, 1-(1,1-dimethylethyl)ester (2.94 g, 14.5 mmol) in THF (20 mL) was added. The mixture was kept at -78°C for 30 minutes and then allowed to warm to room temperature and stirred for 40 minutes. Saturated NH_4Cl was added and the reaction was extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel flash chromatography (30 → 50% EtOAc-CH_2Cl_2) gave a yellow oil (2.14 g). ^{1}H-NMR showed mixture of compounds (two major components). Further purification was not attempted. Used as such in next step.

A portion of the mixture obtained above (0.661 g) and PtO_2 (0.070 g, 0.31 mmol) in EtOH was hydrogenated in a Parr shaker at 48 psi for 2 hours. The mixture was filtered through a Celite pad and the filtrate was concentrated. An additional reaction with the mixture above (1.00 g) was also carried out. Crude products from these reactions were combined and purified by silica gel flash chromatography (1 → 3% MeOH-CH_2Cl_2, then 30% EtOAc-hexanes) to give the title compound (0.192 g, 5.3% overall) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 7.85 (dt, 1H, J=7.6Hz, J=1.8Hz), 7.47-7.56 (m, 1H), 7.09-7.33 (m, 7H), 3.49 (s, 2H), 2.95-3.03 (m, 2H), 2.89 (brd, 2H, J=11.4Hz), 1.94 (brt, 2H, J=11.1Hz), 1.63-1.77 (m, 4H), 1.24-1.39 (m, 3H).

EIMS: 325 (M+), 202, 188, 172, 91, 66 (base).

b) 3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1H-indazole maleate

A mixture of the ketone obtained in step b (0.178 g, 0.55 mmol) in anhydrous hydrazine (10 mL) was heated to reflux for 3 hours. The reaction was allowed to cool, H_2O was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel radial chromatography (CH_2Cl_2 → 10% MeOH-CH_2Cl_2) gave the title compound, free base (0.047 g, 27%) as a colorless oil.

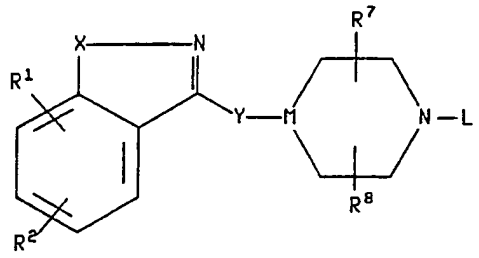
The maleate salt was prepared by adding a solution of maleic acid (0.010 g, 0.085 mmol) in Et_2O (5 mL) to a solution of the free base (0.027 g, 0.085 mmol) in Et_2O (75 mL). The white solid obtained was collected by filtration to give the title compound (0.014 g, 38%).

M.p.: 151.5-152.5°C

^{1}H-NMR (DMSO-d_6) δ 12.64 (s, 1H), 7.72 (d, 1H, J=8.0Hz), 7.44-7.47 (m, 6H), 7.31 (t, 1H, J=7.3Hz), 7.06 (t, 1H, J=7.4Hz), 6.02 (s, 2H), 4.24 (br s, 2H), 2.93 (t, 2H, J=7.6Hz), 1.90-2.00 (m, 2H), 1.60-1.80 (m, 3H), 1.30-1.50 (m, 4H).

CLAIMS

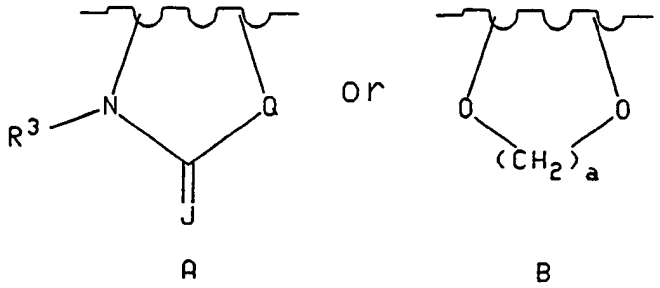
1. A compound of the formula



(I)

wherein R^1 and R^2 are independently selected from hydrogen, (C_1-C_6)alkoxy, benzyloxy, phenoxy, hydroxy, phenyl, benzyl, halo, nitro, cyano, COR^5, $-COOR^5$, $-CONHR^5$, $-NR^5R^6$, $-NR^5COR^6$, $-OCONR^5R^6$, $-NHCOOR^5$, (C_1-C_6)alkyl optionally substituted with from 1 to 3 fluorine atoms; SO_pCH_2-phenyl or $SO_p(C_1-C_6)$alkyl, wherein p is 0, 1 or 2; pyridylmethyloxy or thienylmethyloxy; 2-oxazolyl, 2-thiazolyl and benzenesulfonamide; wherein the phenyl moieties of said phenoxy, benzyloxy, phenyl, benzyl and benzenesulfonamide groups, the pyridyl and thienyl moieties of said pyridylmethyloxy or thienylmethyloxy and the oxazolyl and thiazolyl moieties of said 2-oxaxolyl and 2-thiazolyl may optionally be substituted with 1 or 2 substituents independently selected from halo, (C_1-C_4)alkyl, trifluoromethyl, (C_1-C_4)alkoxy, cyano, nitro and hydroxy;

or R^1 and R^2, when attached to adjacent carbon atoms and when X is oxygen, sulfur or NR^4 wherein R^4 is hydrogen or (C_1-C_4 alkyl) may form, together with the carbon atoms to which they are attached, a group of the formula



A B

wherein J is oxygen, sulfur or NR^4, "a" is 1 or 2, R^3 is hydrogen or (C_1-C_6)alkyl and Q is oxygen, sulfur, NH, $CHCH_3$, $C(CH_3)_2$, -CH=CH-, or $(CH_2)_l$ wherein l is an integer from 1 to 3;

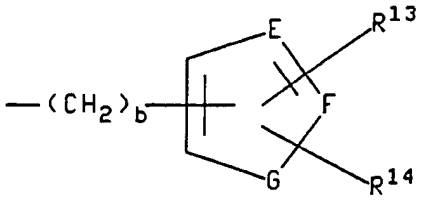
X is oxygen, sulfur, -CH=CH-, -CH=N-, -N=CH-, -N=N-, or NR^4 wherein R^4 is hydrogen or (C_1-C_4) alkyl;

Y is $-(CH_2)_m-$, $-CH=CH(CH_2)_n-$, $-NR^4(CH_2)_m-$, or $-O(CH_2)_m-$ wherein R^4 is defined as above, n is an integer from 0 to 3 and m is an integer from 1 to 3;

R^5 and R^6 are each independently selected from hydrogen, (C_1-C_6)alkyl, phenyl or benzyl, wherein the phenyl moieties of said phenyl and benzyl may optionally be substituted with 1 or 2 substituents independently selected from fluoro, chloro, bromo, iodo, (C_1-C_4) alkyl, trifluoromethyl, (C_1-C_4) alkoxy, cyano, nitro and hydroxy, or NR^5R^6 together form a 4 to 8 membered ring wherein one atom of the ring is nitrogen and the others are carbon, oxygen or nitrogen, or NR^5COR^6 together form a 4 to 8 membered cyclic lactam ring;

M is -CH- or nitrogen;

L is phenyl, phenyl-(C_1-C_6)alkyl, cinnamyl or pyridylmethyl, wherein the phenyl moieties of said phenyl and phenyl-(C_1-C_6)alkyl may optionally be substituted with 1-3 substituents independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkylcarbonyl -$OCONR^5R^6$, $-NHCOOR^5$ or halo; or L is a group of the formula



(K)

wherein b is an integer from 1 to 4, R^{13} and R^{14} are independently selected from hydrogen, (C_1-C_4) alkyl, halo and phenyl, E and F are independently selected from -CH- and nitrogen, and G is oxygen, sulfur or NR^4 wherein R^4 is defined as above, with the proviso that when E and F are both nitrogen, one of R^{13} and R^{14} is absent; and

R^7 and R^8 are independently selected from hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyl and (C_1-C_6)alkoxy, with the proviso that said (C_1-C_6)alkoxy is not attached to a carbon that is adjacent to a nitrogen;

or pharmaceutically acceptable salt of such compound.

2. A compound according to claim 1, wherein X is sulfur or oxygen, Y is $-CH_2-CH_2-$, or $-CH_2-$, M is -CH- and L is benzyl, R^1 and R^2 are (C_1-C_6)alkyl, (C_1-C_6)alkoxy, NR^5R^6, or NR^5COR^6, R^3 is hydrogen or (C_1-C_6)alkyl, J is oxygen or sulfur and Q is $CH(CH_3)$, $CH(CH_3)_2$, -CH=CH or $(CH_2)_1$.

3. A compound selected from the group consisting of:

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5-Methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5,6-Dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

7-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Acetamido-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Benzamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Benzenesulfonamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-(4-Morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5,7-Dihydro-3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

1-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-isoquinoline;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisothiazole;

4-[2-[1-(Phenylmethyl)-4-piperidnyl]ethyl]-1,3-quinazoline;

6-Hydroxy-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Bromo-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Cyano-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Carboxamide-3-[2-[1-(phenylmethyl)-4-piperidyl]-ethyl]-1,2-benzisoxazole;

3-[(1-Phenylmethyl-4-piperidyl)methoxy]-1,2-benzisoxazole;

3-[(1-Phenylmethyl-4-piperidyl)methylamino]-1,2-benzisoxazole;

3-[2-(1-Phenylmethyl)-4-piperidyl)ethylamino]-1,2-benzisoxazole;

3-[3-[1-(Phenylmethyl)-4-piperidyl]propyl]-1,2-benzisoxazole;

trans-3-[2-[1-(Phenylmethyl)-4-piperidyl]ethenyl]-1,2-benzisoxazole;

3-[2-[1-(Phenylmethyl)-4-piperazinyl]ethyl]-1,2-benzisoxazole;

5,7-Dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-7-ethyl-3-[2[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(2-chloro-5-thiophenemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(2-methyl-4-thiazolemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(3-Bromophenylmethyl)-4-piperidinyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(4-Bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]-propyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-5,6,8-trihydro-7H-isoxazolo[4,5-g]quinolin-7-one;

6,8-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one;

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-6H-pyrrolo[5,4-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1H-indazole;

and the pharmaceutically acceptable salts of such compounds.

4. A compound according to claim 1, selected from the group consisting of:

3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate;

5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole maleate;

5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate;

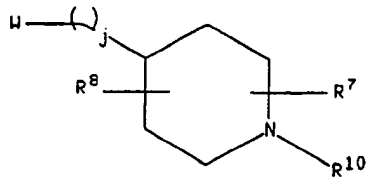
7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole fumarate;

6-benzamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole maleate;

6-benzenesulfonamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole fumarate; and

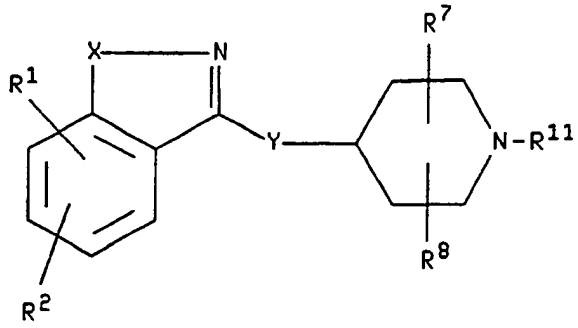
1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]isoquinoline maleate.

5. A compound of the formula



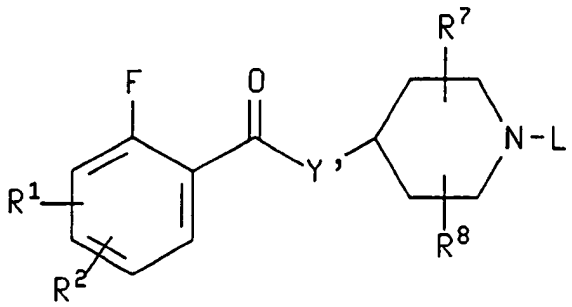
wherein W is a leaving group; j is an integer from 0 to 2; R^{10} is a nitrogen protecting group; and R^7 and R^8 are independently selected from hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyl and (C_1-C_6)alkoxy, with the proviso that said (C_1-C_6)alkoxy is not attached to a carbon that is adjacent to a nitrogen.

6. A compound of the formula



wherein R^1, R^2, R^7, R^8, X, Y and M are as defined in claim 1 and R^{11} is hydrogen or a nitrogen protecting group.

7. A compound of the formula



wherein R^1, R^2, R^7, R^8 and L are as defined in claim 1 and Y' is $-CH=CH-(CH_2)_n-$or$-(CH_2)_m-$.

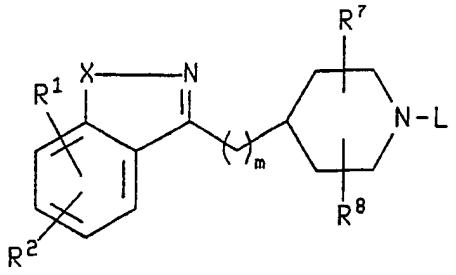
8. A pharmaceutical composition for enhancing memory or treating or preventing Alzheimer's disease comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition for inhibiting cholinesterase in a mammal, comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

10. A method of inhibiting cholinesterase in a mammal, comprising administering to a mammal a cholinesterase inhibiting amount of a compound according to claim 1.

11. A method of enhancing memory or treating or preventing Alzheimer's disease, comprising administering to a patient a memory enhancing effective amount of a compound according to claim 1.

12. A process for preparing a compound having the formula

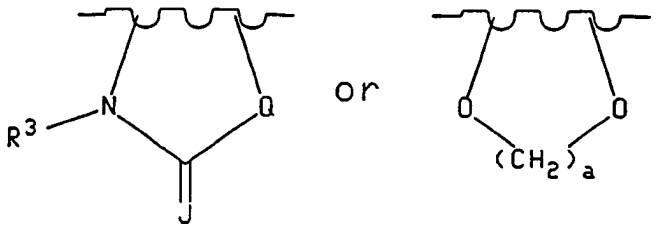


I-A

wherein R^1 and R^2 are independently selected from hydrogen, (C_1-C_6)alkoxy, benzyloxy, phenoxy, hydroxy, phenyl, benzyl, halo, nitro, cyano, COR^5, $-COOR^5$, $-CONHR^5$, $-NR^5R^6$, $-NR^5COR^6$, $-OCONR^5R^6$, $-NHCOOR^5$, (C_1-C_6)alkyl optionally substituted with from 1 to 3 fluorine atoms; SO_pCH_2-phenyl or $SO_p(C_1-C_6)$alkyl, wherein p is 0, 1 or 2; pyridylmethyloxy or thienyl-methyloxy; 2-oxazolyl, 2-thiazolyl and benzenesulfonamide; wherein the phenyl moieties of said phenoxy, benzyloxy, phenyl, benzyl and benzenesulfonamide groups, the pyridyl and thienyl moieties of said pyridylmethyloxy or thienylmethyloxy and the oxazolyl and

thiazolyl moieties of said 2-oxaxolyl and 2-thiazolyl may optionally be substituted with 1 or 2 substituents independently selected from halo, (C_1-C_4)alkyl, trifluoromethyl, (C_1-C_4)alkoxy, cyano, nitro and hydroxy;

or R^1 and R^2, when attached to adjacent carbon atoms and when X is oxygen, sulfur or NR^4 wherein R^4 is hydrogen or (C_1-C_4 alkyl) may form, together with the carbon atoms to which they are attached, a group of the formula



A B

wherein J is oxygen, sulfur or NR^4, "a" is 1 or 2, R^3 is hydrogen or (C_1-C_6)alkyl and Q is oxygen, sulfur, NH, $CHCH_3$, $C(CH_3)_2$, -CH=CH-, or $(CH_2)_l$ wherein l is an integer from 1 to 3;

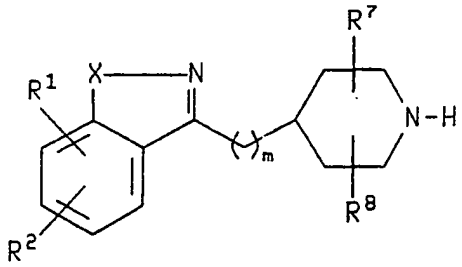
X is oxygen, sulfur, -CH=CH-, -CH=N-, -N=CH-, -N=N-, or NR^4 wherein R^4 is hydrogen or (C_1-C_4) alkyl;

m is an integer from 1 to 3;

R^7 and R^8 are independently selected from hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyl and (C_1-C_6)alkoxy, with the proviso that said (C_1-C_6)alkoxy is not attached to a carbon that is adjacent to a nitrogen;

L is phenyl-(C_1-C_6)alkyl, pyridylmethyl, or a group of the formula K;

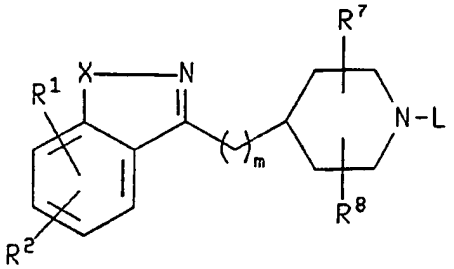
or a pharmaceutically acceptable acid addition salt thereof; comprising: (a) reacting a compound of formula



VI

wherein R^1, R^2, X, m, R^7, and R^8 are defined as above with a compound of formula WL wherein W is a leaving group and L is defined as above; and (b) optionally reacting the compound of formula I-A obtained thereby with a pharmaceutically acceptable salt.

13. A process for preparing a compound having the formula



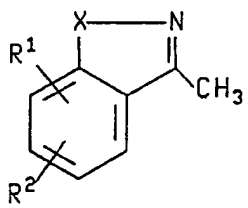
I-B

wherein R^1, R^2, X, m, R^7 and R^8 are defined as in claim 12;

L is phenyl or cinnamyl;

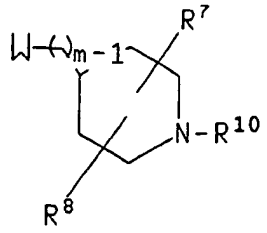
or a pharmaceutically acceptable acid addition salt thereof;

comprising: (a) reacting a compound of formula



II

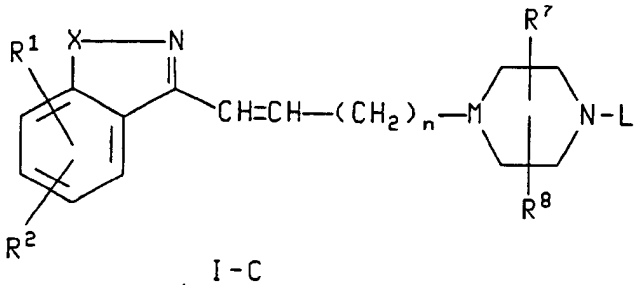
wherein R^1, R^2, and X are defined as in claim 12 with a compound of the formula



III

wherein W, m, R^7 and R^8 are defined as in claim 12, and R^{10} is L as defined above; and (b) optionally reacting the compound of formula I-B obtained thereby with a pharmaceutically acceptable salt.

14. A process for preparing a compound having the formula



I-C

wherein R^1, R^2, X, R^7 and R^8 are defined as in claim 12;

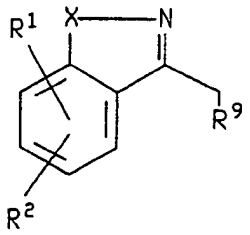
n is an integer from 0 to 3;

M is nitrogen or -CH-;

L is phenyl, cinnamyl, phenyl-(C_1-C_6)alkyl, pyridylmethyl, or a group of the formula K;

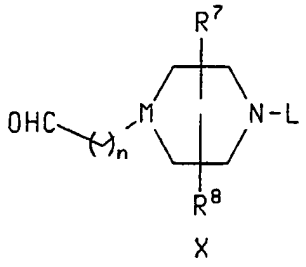
or a pharmaceutically acceptable acid addition salt thereof;

comprising: (a) reacting a compound of formula



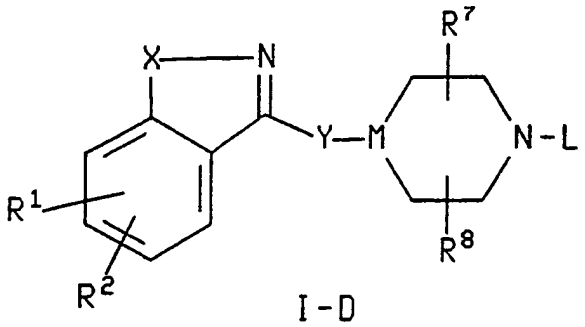
IX

wherein R^1, R^2 and X are defined as in claim 12, R^9 is hydrogen or halo with a compound of the formula



wherein R^7 and R^8 are defined as in claim 12, and n, M and L are defined as above; and (b) optionally reacting the compound of formula I-C obtained thereby with a pharmaceutically acceptable salt.

15. A process for preparing a compound having the formula



I-D

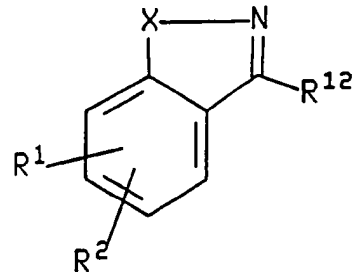
wherein R^1, R^2, X, R^7, R^8 and L are defined as in claim 12;

M is defined as in claim 14;

Y is $-(CH_2)_m-$, $-CH=CH(CH_2)_n-$, $-NR^4(CH_2)_m-$, or $-O(CH_2)_m-$ wherein R^4 is defined as above, n is an integer from 0 to 3 and m is an integer from 1 to 3;

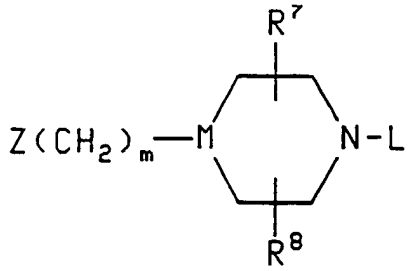
or a pharmaceutically acceptable acid addition salt thereof;

comprising: (a) reacting a compound of formula



XI

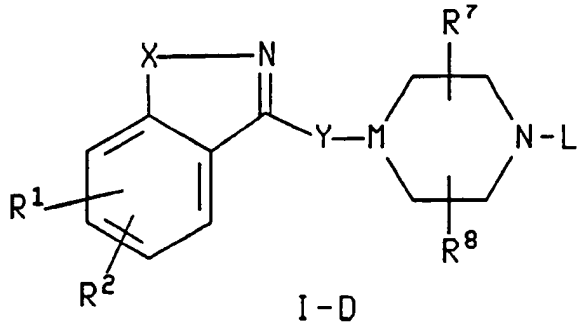
wherein R^1, R^2 and X are defined as in claim 12, R^{12} is halo with a compound of the formula



XII

wherein m, R^7 and R^8 are defined as in claim 12, M and L are defined as in claim 14, and Z is OH or NHR^4 wherein R^4 is hydrogen or (C_1-C_4)alkyl; and (b) optionally reacting the compound of formula I-D obtained thereby with a pharmaceutically acceptable salt.

16. A process for preparing a compound having the formula



I-D

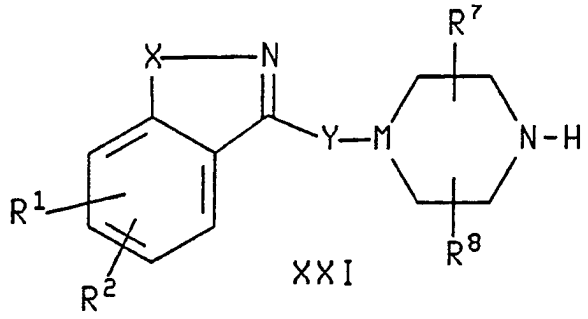
wherein R^1, R^2, X, R^7 and R^8 are defined as in claim 12;

M and L are defined as in claim 14;

Y is defined as in claim 15;

or a pharmaceutically acceptable acid addition salt thereof;

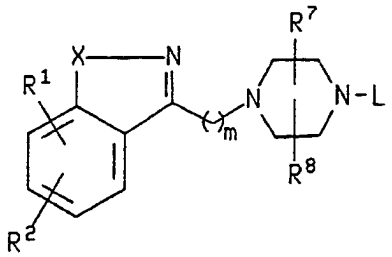
comprising: (a) reacting a compound of formula



XXI

wherein R^1, R^2, X, R^7 and R^8 are defined as in claim 12, M is defined as in claim 3, and Y is defined as in claim 15 with a compound of the formula WL wherein W and L are defined as in claim 12, and (b) optionally reacting the compound of formula I-D obtained thereby with a pharmaceutically acceptable salt.

17. A process for preparing a compound having the formula



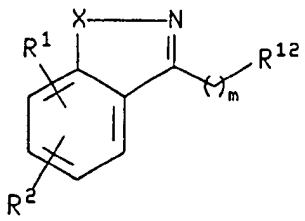
I-E

wherein R^1, R^2, X, m, R^7 and R^8 are defined as in claim 12;

L is defined as in claim 14;

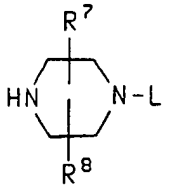
or a pharmaceutically acceptable acid addition salt thereof;

comprising: (a) reacting a compound of formula



XIII

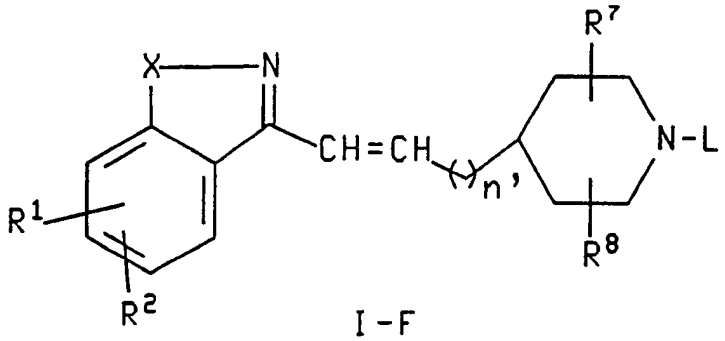
wherein R^1, R^2 and X are defined as in claim 12 and R^{12} is halo with a compound of the formula



XIV

wherein R^7 and R^8 are defined as in claim 12, and L is defined as in claim 14; and (b) optionally reacting the compound of formula I-E obtained thereby with a pharmaceutically acceptable salt.

18. A process for preparing a compound having the formula



I-F

wherein R^1, R^2, R^7 and R^8 are defined as in claim 12;

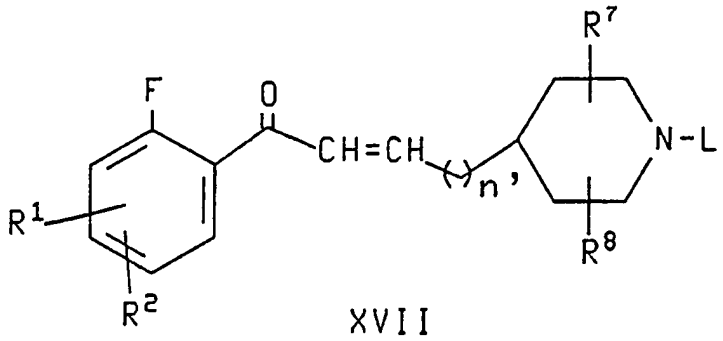
L is defined as in claim 14;

X is oxygen or NR^4 wherein R^4 is defined as in claim 15;

n' is an integer from 0 to 3;

or a pharmaceutically acceptable acid addition salt thereof;

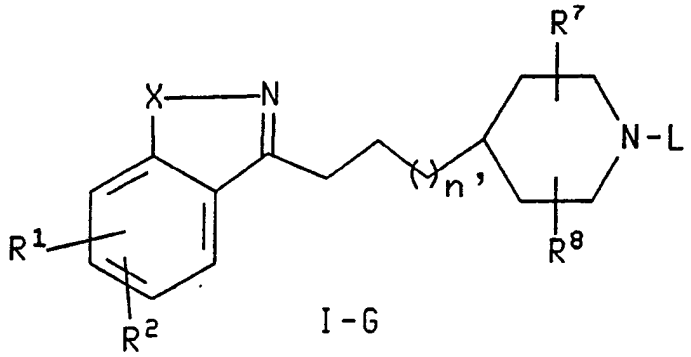
comprising: (a) reacting a compound of formula



XVII

wherein R^1, R^2, R^7 and R^8 are defined as in claim 12, L is defined as in claim 14, and n' is defined as above with hydrazines or hydroxylamines; and (b) optionally reacting the compound of formula I-F obtained thereby with a pharmaceutically acceptable salt.

19. A process for preparing a compound having the formula



I-G

wherein R^1, R^2, R^7 and R^8 are defined as in claim 12;

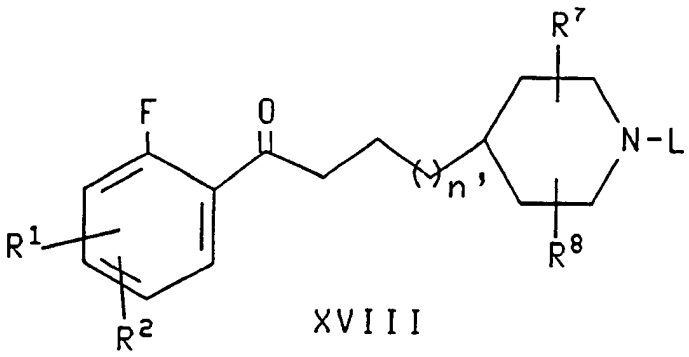
L is defined as in claim 14;

X is defined as in claim 18;

n' is an integer from 0 to 1;

or a pharmaceutically acceptable acid addition salt thereof;

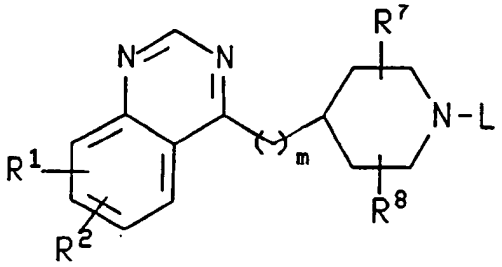
comprising: (a) reacting a compound of formula



XVIII

wherein R^1, R^2, R^7 and R^8 are defined as in claim 12, L is defined as in claim 14, and n' is defined as above with hydrazines or hydroxylamines; and (b) optionally reacting the compound of formula I-G obtained thereby with a pharmaceutically acceptable salt.

20. A process for preparing a compound having the formula

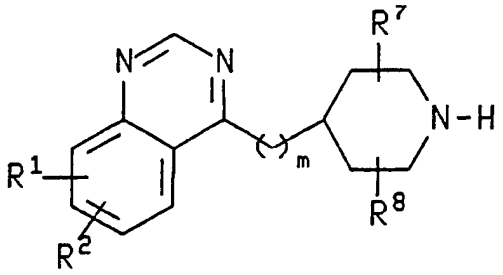


I-H

wherein R^1, R^2, m, R^7, R^8 and L are defined as in claim 12;

or a pharmaceutically acceptable acid addition salt thereof;

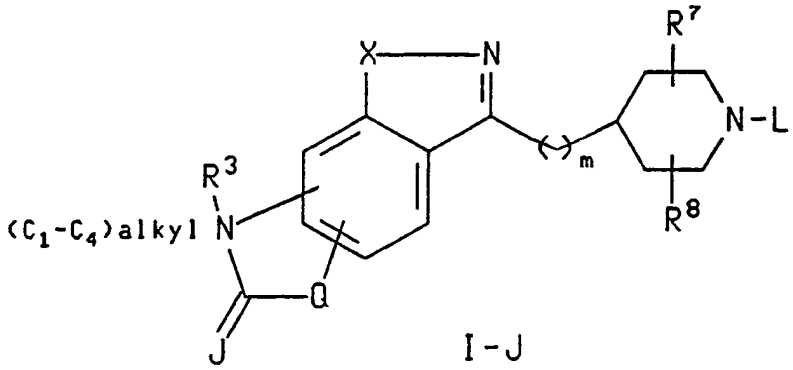
comprising: (a) reacting a compound of formula



VI'

wherein R^1, R^2, m, R^7 and R^8 are defined as in claim 12 with a compound of formula WL wherein W and L are defined as in claim 12; and (b) optionally reacting the compound of formula I-H obtained thereby with a pharmaceutically acceptable salt.

21. A process for preparing a compound having the formula



I-J

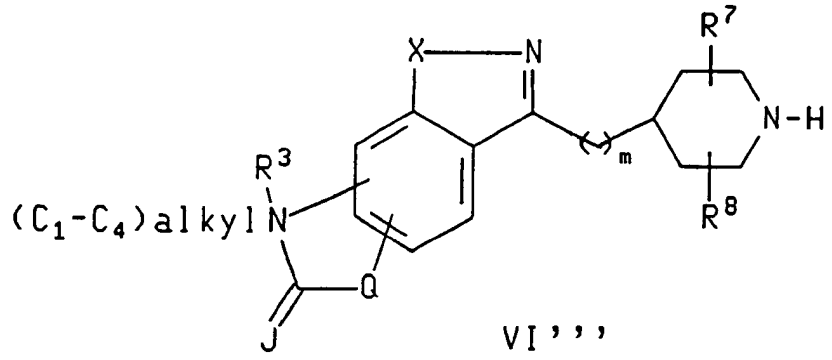
wherein m, R^7, R^8 and L are defined as in claim 12;

X and J are oxygen, sulfur, or NR^4 wherein R^4 is defined as in claim 15;

Q is oxygen, sulfur, NH, $CHCH_3$, $C(CH_3)_2$, -CH=CH-, or $(CH_2)_1$ wherein 1 is an integer from 1 to 3;

or a pharmaceutically acceptable acid addition salt thereof;

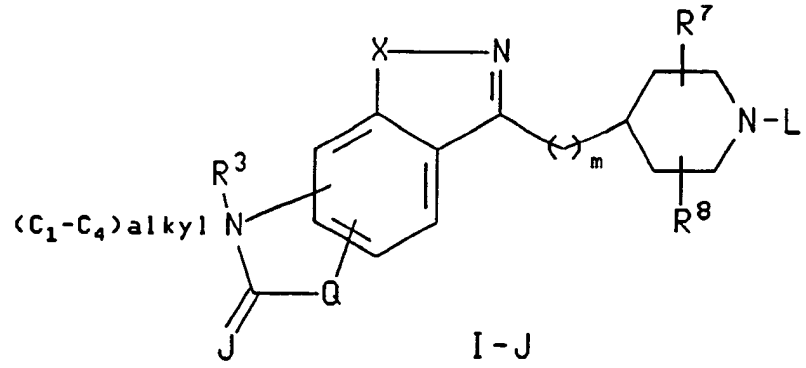
comprising: (a) reacting a compound of formula



VI'''

wherein m, R^7 and R^8 are defined as in claim 12, and X, J and q are defined as above with a compound of formula WL wherein W and L are defined as in claim 12; and (b) optionally reacting the compound of formula I-J obtained thereby with a pharmaceutically acceptable salt.

22. A process for preparing a compound having the formula



I-J

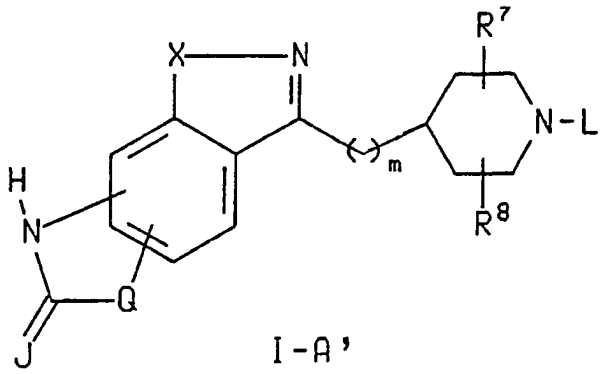
wherein m, R^7 and R^8 are defined as in claim 12;

L is defined as in claim 14;

X, J and Q are defined as in claim 21;

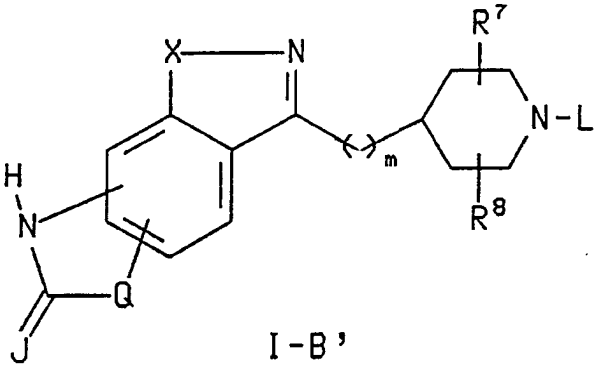
or a pharmaceutically acceptable acid addition salt thereof;

comprising: (a) reacting a compound of formula



I-A'

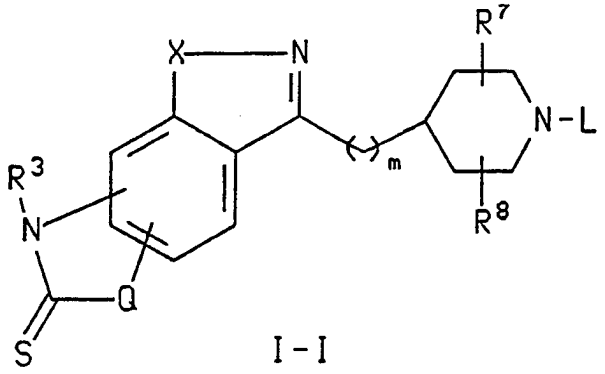
wherein m, R^7, R^8 and L are defined as in claim 12, X, J, and Q are defined as in claim 21, or a compound of the formula



I-B'

wherein m, R^7, and R^8 are define as in claim 12, L is defined as in claim 13, X, J and Q are defined as in claim 21 with an alkylating agent of formula (C_1-C_4)alkyl-W wherein W is defined as in claim 12; and (b) optionally reacting the compound of formula I-J obtained thereby with a pharmaceutically acceptable salt.

23. A process for preparing a compound having the formula



I-I

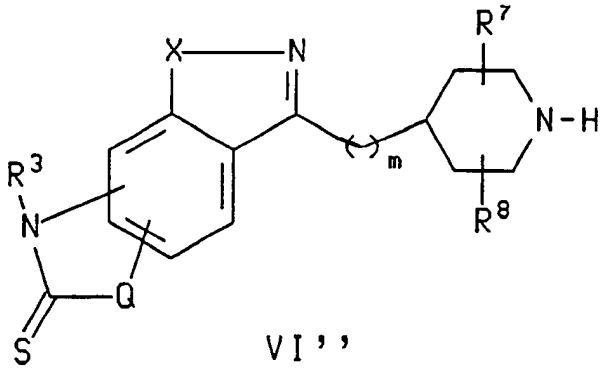
wherein m, R^7, R^8 and L are defined as in claim 12;

X and Q are defined as in claim 21;

R^3 is (C_1-C_6)alkyl;

or a pharmaceutically acceptable acid addition salt thereof;

comprising: (a) reacting a compound of formula



VI''

wherein m, R^7 and R^8 are defined as in claim 12, X and Q are defined as in claim 21, and R^3 is defined as above with a compound of the formula WL wherein W and L are defined as in claim 12; and (b) optionally reacting the compound of formula I-I obtained thereby with a pharmaceutically acceptable salt.

24. A process according to any of the preceding claims wherein X is sulfur or oxygen, Y is $-CH_2-CH_2-$, or $-CH_2-$, M is -CH- and L is benzyl, R^1 and R^2 are (C_1-C_6)alkyl, (C_1-C_6)alkoxy, NR^5R^6, or NR^5COR^6, R^3 is hydrogen or (C_1-C_6)alkyl, J is oxygen or sulfur and Q is $CH(CH_3)$, $CH(CH_3)_2$, -CH=CH or $(CH_2)_1$.

25. A process according to any of the preceding claims wherein said compound is selected from the group consisting of:

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5-Methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5,6-Dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

5-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

7-Methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Acetamido-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

6-Amino-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-Benzamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole;

6-Benzenesulfonamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

6-(4-Morpholinyl)-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole;

5,7-Dihydro-3-[2-[1-(Phenylmethyl)-4-piperidinyl]-ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

1-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-isoquinoline;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisothiazole;

4-[2-[1-(Phenylmethyl)-4-piperidnyl]ethyl]-1,3-quinazoline;

6-Hydroxy-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Bromo-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Cyano-3-[2-[1-(phenylmethyl)-4-piperidyl]ethyl]-1,2-benzisoxazole;

6-Carboxamide-3-[2-[1-(phenylmethyl)-4-piperidyl]-ethyl]-1,2-benzisoxazole;

3-[(1-Phenylmethyl-4-piperidyl)methoxy]-1,2-benzisoxazole;

3-[(1-Phenylmethyl-4-piperidyl)methylamino]-1,2-benzisoxazole;

3-[2-(1-Phenylmethyl)-4-piperidyl)ethylamino]-1,2-benzisoxazole;

3-[3-[1-(Phenylmethyl)-4-piperidyl]propyl]-1,2-benzisoxazole;

trans-3-[2-[1-(Phenylmethyl)-4-piperidyl]ethenyl]-1,2-benzisoxazole;

3-[2-[1-(Phenylmethyl)-4-piperazinyl]ethyl]-1,2-benzisoxazole;

5,7-Dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-7-ethyl-3-[2[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(2-chloro-5-thiophenemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[2-[1-(2-methyl-4-thiazolemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(3-Bromophenylmethyl)-4-piperidinyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(4-Bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-Dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]-propyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-5,6,8-trihydro-7H-isoxazolo[4,5-g]quinolin-7-one;

6,8-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one;

5,7-Dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-6H-pyrrolo[5,4-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(Phenylmethyl)-4-piperidinyl]ethyl]-1H-indazole;

and the pharmaceutically acceptable salts of such compounds.

26. A process according to any of the preceding claims wherein said compound is selected from the group consisting of:

3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate;

5,6-dimethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole maleate;

5-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole maleate;

7-methoxy-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole fumarate;

6-benzamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]-ethyl]-1,2-benzisoxazole maleate;

6-benzenesulfonamide-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole fumarate; and

1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]isoquinoline maleate.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01605

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 413/06 A 61 K 31/445 C 07 D 498/04
C 07 D 401/06 C 07 D 417/06 C 07 D 261/20 C 07 D 413/12
C 07 D 211/32

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP,A,0296560 (EISAI CO., LTD) 28 December 1988, see the claims	1,8-11
Y	EP,A,0091511 (HOECHST ROUSSEL) 19 October 1983, see the claims	1,8-11
Y	EP,A,0229391 (EISAI CO., LTD) 22 July 1982, see the claims	1,8-11
P,X	EP,A,0428437 (ADIR ET COMPAGNIE) 22 May 1991, see the claims	1,8-11

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23-07-1992	19. 08. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

I. national application No.

PCT/US92/01605

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 10 and 11 are directed to a method of treatment of human body, the search has been carried out and based on the alleged effects of the compounds.

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Remark: In claim 5 the definition of the variables W and R_{10} are vague and do not concisely define the matter for which protection is sought so that a comprehensive search is not possible

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201605 SA 60166

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/08/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0296560	28-12-88	JP-A- 1079151	24-03-89
		US-A- 4895841	23-01-90
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		AU-A- 6581990	16-05-91
		CA-A- 2029372	08-05-91
		JP-A- 3188077	16-08-91
		US-A- 5100902	31-03-92